Universidade de Aveiro Secção Autónoma de Ciências da Saúde
2013

ANA RITA MARQUES RIBEIRO

ESTÁGIO CURRICULAR NUM CENTRO DE COORDENAÇÃO DE INVESTIGAÇÃO CLÍNICA

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Relatório final de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica da Drª Sandrina Gonçalves Nunes, Diretora do Centro de Coimbra de Coordenação de Investigação Clínica, da Associação para Investigação Biomédica e Inovação em Luz e Imagem, e da Professora Doutora Maria Joana da Costa Gomes da Silva da Escola Superior de Saúde da Universidade de Aveiro.

Curricular training report presented to the University of Aveiro to fulfill the necessary requirements for the Master's Degree in Pharmaceutical Medicine, held under the scientific guidance of Drª Sandrina Gonçalves Nunes, Director of Coimbra Coordinating Centre for Clinical Research pertaining to Association for Innovation and Biomedical Research on Light and Image and Professor Maria Joana da Costa Gomes da Silva, School of Health, University of Aveiro.

Dedico este trabalho às pessoas mais importantes na minha vida.
Pelo que me ensinaram e transmitiram.
Pelo apoio incondicional e incessante.
Pelo que sou.

Sem eles nenhum sonho seria possível nem valeria a pena.

Aos meus pais, às minhas avós e ao meu irmão.
Ao meu namorado.
À minha família.
Aos meus amigos.

o júri
presidente

Prof. Doutor José Luís de Almeida
Professor Associado Convidado da Escola Superior de Saúde da Universidade de Aveiro

Prof. Doutor Bruno Miguel Alves Fernandes do Gago
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agradecimentos

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palavras-chave

Estágio, CRO, aCRO, Ensaios Clínicos da Iniciativa do Investigador, IDCT, Ensaios Clínicos, Projectos de Investigação, Gestão de Projeto, Biomedicina Farmacêutica,Oftalmologia

resumo

Este relatório descreve as actividades desenvolvidas durante o meu estágio curricular como assistente de gestor de projecto, no Centro de Coimbra de Coordenação de Investigação Clínica, 4C, uma *academic contract reseach organisation* (aCRO). É um centro de investigação pertencente à Associação para Investigação Biomédica e Inovação em Luz e Imagem, AIBILI.

O estágio decorreu entre 8 de outubro de 2012 a 7 de junho de 2013 e teve como principal objectivo adquirir ferramentas de trabalho e competências na área de gestão de projecto que me possibilitem integrar o mercado actual de trabalho.

Além dos serviços que presta à indústria farmacêutica, o 4C atua como uma aCRO apoiando o desenvolvimento e a coordenação de Ensaios Clínicos da Iniciativa do Investigador (IDCTs). Assim, dos 11 projetos de investigação em que estive envolvida, 10 foram IDCTs. Neste documento é apresentada uma caracterização sobre o estado da arte dos IDCTs.

Como assistente de gestor de projectos num centro de investigação clínica pude participar em diversas actividades de diferentes âmbitos: elaboração de documentos de estudo, planeamento e validação de um caderno de recolha de dados (CRD) electrónico, introdução e validação de dados, avaliação da exequibilidade de centros de ensaio, gestão de dados, gestão de estudos clínicos e arquivo e gestão de documentação de estudos clínicos. Tive ainda a oportunidade de apoiar o monitor de estudo em actividades relacionadas com o final da fase clínica de um ensaio.

Além das tarefas desempenhadas, recebi treino genérico na área de especialidade da AIBILI – oftalmologia. Entre formações e seminários, tive a oportunidade de participar num curso sobre a degenerescência da mácula relacionada com a idade e angiogénese, de 15 horas.

O ambiente multidisciplinar das actividades realizadas no 4C permitiram-me adquirir um conhecimento mais abrangente sobre o ciclo de vida de um projeto de investigação. Especificamente, a participação em actividades de desenho, implementação, condução e coordenação de um projecto de investigação clínica permitiu-me valorizar o papel fundamental de um gestor de projecto nestes processos.

A experiencia adquirida neste estágio curricular foi muito enriquecedora. Através de uma participação ativa nas diversas actividades praticadas pelo 4C, adquiri competências pessoais e profissionais que no futuro irão possibilitar trabalhar nesta área. O estágio também me permitiu integrar conhecimentos adquiridos no Mestrado em Biomedicina Farmacêutica nas diversas actividades de investigação clínica realizadas.

Termino este estágio com a motivação e certeza que gostaria de integrar o mercado de trabalho na área de gestão de projecto.

keywords

Internship, CRO, aCRO, Investigator-Driven Clinical Trials, IDCT, Clinical Trials, Research Projects, Project Management, Pharmaceutical Medicine, Ophthalmology

abstract

This report describes my curricular internship activities performed as a project manager assistant at the Coimbra Coordinating Centre for Clinical Research, 4C, an academic Contract Research Organisation (aCRO). It is a Research Centre pertaining to Association for Innovation and Biomedical Research on Light and Image, AIBILI.

The internship occurred from 8th October 2012 to 7th June 2013 and had as a major objective to acquire specific working tools and competencies in the project management area that enables me to integrate the current labor market.

Besides providing services to pharmaceutical industry, as an aCRO 4C supports the development and coordination of Investigator-Driven Clinical Trials (IDCTs). Due to this fact, of the 11 clinical projects that I was involved, 10 were IDCTs. In this document, a characterization of the state of the art on IDCTs is presented.

As a project manager assistant in a clinical research coordinating centre I could participate in several activities from different contexts: study documents elaboration, planning and validation of an electronic case report form (eCRF), data entry and validation, feasibility assessment, study and data management and archiving and managing clinical trial documentation. In addition, I could assist the study monitor in end of clinical-trial related activities.

Additionally to the on-the-job activities, I receive a generic training concerning the area of expertise of AIBILI – ophthalmology. Between training sessions and workshops, I had the opportunity to attend a training course of 15 hours regarding age-related macular degeneration and angiogenesis.

The multidisciplinary framework of the activities performed at 4C has enabled me to acquire a more comprehensive knowledge of a clinical project's lifecycle. Particularly, participating in the design, implementation, conduction and coordination of a clinical research project enabled me to understand the central role of a project manager in a clinical study.

The experience taken from this curricular internship was very enriching to me. As I accomplish to develop an active participation through the activities carried out by 4C, I developed personal skills and acquired professional competencies which, in the future, allow me to work in this area. It was also possible to integrate into clinical research activities the background knowledge from the Master course in Pharmaceutical Medicine.

I complete this curricular training with the motivation and certain that I would like to work as a project manager in the future.

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Abbreviations List

4C	Coimbra Coordinating Centre for Clinical Research
aCRO	Academic Contract Research Organisation
AIBILI	Association for Innovation and Biomedical Research on Light and Image
AMC	Academic Medical Centre
AMD	Age-Related Macular Degeneration
CEC	Clinical Trial Centre
CEO	Chief Executive Officer
CFP	Color Fundus Photography
CHAD	Health Technology Assessment and Drug Research
CHUC	Coimbra Hospital and University Centre
CNTM	Centre of New Technologies for Medicine
CORC	Coimbra Ophthalmology Reading Centre
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Application
C-TRACER	Champalimaud Translational Centre for Eye Research
DR	Diabetic Retinopathy
eCRF	Electronic Case Report Form
ECRIN	European Clinical Research Infrastructures Network
EDC	Electronic Data Capture
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials

EVICR.net	European Vision Institute Clinical Research Network
GCP	Good Clinical Practices
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use
IDCT	Investigator-Driven Clinical Trial
IMP	Investigational Medicinal Product
INFARMED	National Authority of Medicines and Health Products P.I.
ISO	International Organisation for Standardisation
LHON	Leber's Hereditary Optic Nerve Disease
OCT	Optical Coherence Tomography
OECD	Organisation for Economic Co-operation and Development
PtCRIN	Portuguese Clinical Research Infrastructure Network
R&D	Research and Development
RTO	Research Technology Organisation

Introduction

From 8th October 2012 to 7th June 2013 I had the opportunity to complete my Master's Degree in Pharmaceutical Medicine attending a curricular internship at Coimbra Coordinating Centre for Clinical Research (4C), an academic contract research organisation (aCRO) of Association for Innovation and Biomedical Research on Light and Image (AIBILI).

My training report is the compilation of all activities performed in 4C. This report is organised in five chapters. The first chapter is an introduction to contextualise the training and to present its structure that includes a characterisation of the host institution, my training objectives and a description about the state-of-the-art on Investigator-Driven Clinical Trials (IDCTs) and the importance of aCROs. During my training, most of all clinical research projects that I was involved were IDCTs. Due to this fact, the state-of-the-art will address IDCTs by:

- Introducing some definitions and particularities of IDCTs,
- Describing the necessity for conducting IDCTs, enunciating the advantages of academic partnerships;
- Describing the current European and Portuguese status of activity of investigator-initiated clinical research;
- Describing the current obstacles needed to overpass to conduct IDCTs in Europe.

The second chapter is the generic training where I described the training sessions, workshops and a training course attended at AIBILI. The specific training refers to the activities performed at 4C, and is the third chapter. The final two chapters refer to a discussion of my training experience and finally some conclusions are drawn from this training period.

This training report will also include two annexes representing an important task carried out in the specific training, responsible for the implementation of a new tool to manage and send questionnaires. These are a comparative document concerning Lime Survey and Monkey Survey characteristics and a Lime Survey user manual.

For the purpose of this training report, the term IDCT includes all clinical trials initiated by academic and non-academic researchers with non-commercial interests.

1.1. Vision of the Host Institution

AIBILI is a private, non-profit, Research Technology Organization (RTO). The core mission of this type of organizations is to explore science and technology in the service of innovation, to improve quality of life and built economic competitiveness. RTOs bring together key players across the whole innovation chain, from basic to technological research, from product and process development to prototyping and demonstration. RTOs are generally non-profit organizations in which revenues from dissemination and deployment are re-employed to fund new innovation cycles (1, 2).

In an historical context, AIBILI was established to support technology transfer between academic institutions and the industry and to give patients access to the most recent results of biomedical research. It was founded in 1989, initially with the support of the Ministry of Economy's through the program *Programa Específico de Desenvolvimento da Indústria Portuguesa*. It is located at the Health Campus of Coimbra University since 1994 (1, 3).

Since 2004, AIBILI is certified by International Organisation for standardisation (ISO) 9001 standard and clinical trials are performed in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice Guidelines (ICH-GCP) and the pharmacology studies are also developed in compliance with the Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (GLP) (1).

AIBILI is organized in Research Centres and Structural Units. The Research Centres are: 4C, European Vision Institute Clinical Research Network (EVICR.net), Coimbra Ophthalmology Reading Centre (CORC), Health Technology Assessment and Drug Research (CHAD), Clinical Trial Centre (CEC) and Centre of New Technologies for Medicine (CNTM). The Structural Units are: Quality Management, Administrative Services, Translational Research and Technology Transfer and Information Technology. Table 1 and Table 2 present a brief description of the main activities performed at each Research Centre and Supporting Unit (1, 4).

Table 1 – Research Centres of AIBILI and their main activities in 2013 (1, 4).

Research Centre	Main activity(ies)
4C	Structure to support the development and coordination of Investigator-Driven and Industry-Sponsored Clinical Trials. 4C is also the coordinating centre of the EVICR.net.
EVICR.net	European network for clinical research in ophthalmology, created in 2010. At present, EVICR.net has 79 members from 16 European Countries.
CORC	Structure for grading ophthalmological images such as CFP and OCT images of the retina and functional evaluations of retina using multifocal electroretinogram.
CHAD	Evaluates medicines and other medical products for market access purposes, aiming at financing and reimbursement, performs pharmacovigilance and bioequivalence studies for generic drugs approval and drug safety monitoring.
CEC	Performs clinical trials with special emphasis on ophthalmology and neurology.
CNTM	Develops new medical diagnostic techniques with special emphasis on the area of eye fundus imaging.

CFP – Colour Fundus Photography; OCT – Optical Coherence Tomography

Table 2 – Structural Units of AIBILI and their main activities in 2013 (1, 4).

Structural Unit	Main Activity (ies)
Quality Management	Assure that quality management system is maintained effective and efficient, permitting a continual improvement and that the services provided by AIBILI are valid and reliable.
Administrative Services	Management of AIBILI and all related administrative tasks, including finances, human resources management and maintenance of the infrastructure.
Translational Research and Technology Transfer	Management of external contracts and partnerships, acquisition of external funding, promotion of AIBILI as well as the activities and services of its Research Centres.
Information Technology	Guarantees the safety and integrity of the data and images collected. Management and maintenance of the electronic medical records of the CEC that is daily used to collect patient data and the platform of CORC used to exchange data and images. This Structural Unit is under the responsibility of CNTM.

The organogram of AIBILI is presented in Figure 1. The Board of Directors is constituted by the President José Cunha-Vaz, Vice-President Joaquim Murta, Tice Macedo representing BIAL – Portela & Cª, SA, João Silveira Botelho representing Champalimaud Foundation, Conceição Lobo

representing José Cotta – EMS, SA, Cristina Morgado representing Novartis Farma and José Aleixo Dias representing Pfizer Laboratories (1).

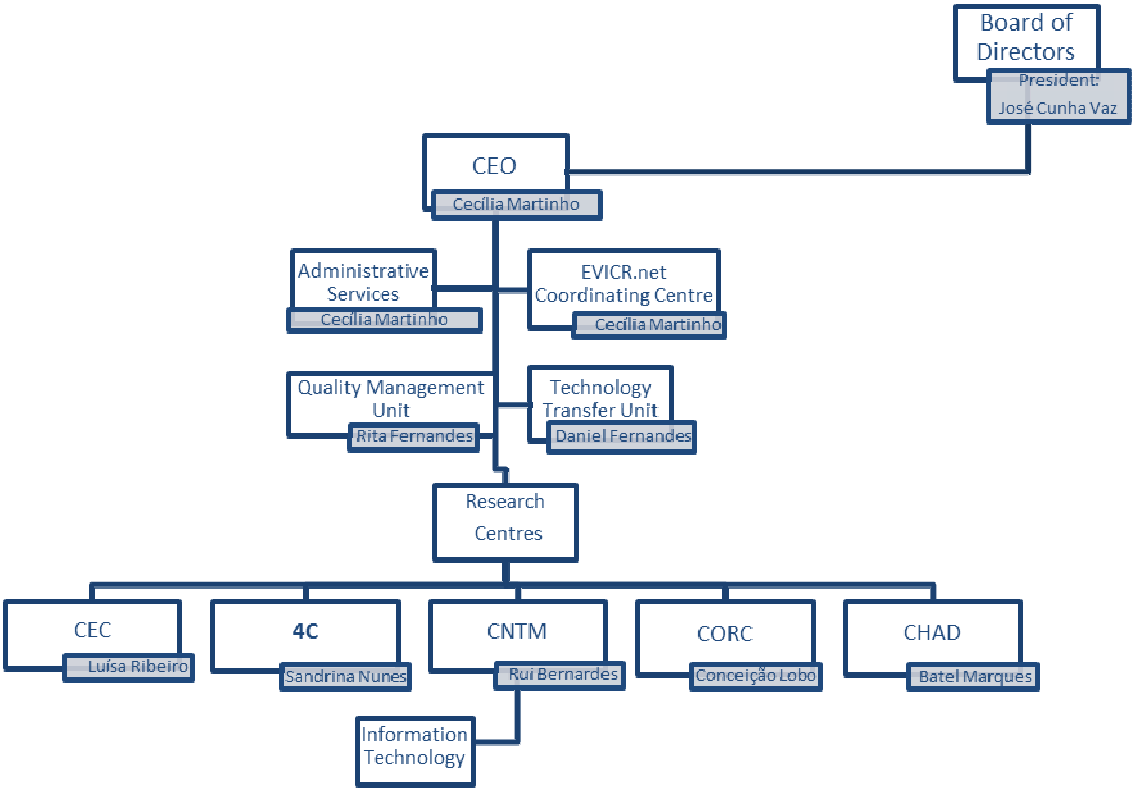

Figure 1 – Organisational structure of AIBILI with the responsible of each Research Centre and Structural Unit (1). CEO – Chief Executive Officer.

Concerning AIBILI's financial status, its activity is mainly supported by services to industry. Examples of actual industry clients are Novartis, Bayer, Pfizer, Sanofi-Aventis, between others. Public funding is present essentially in Research and Development (R&D) projects financed by Portuguese Foundation for Science and Technology as well as the European Commission. The financial evolution of AIBILI in the last five years is represented by the Figure 2 (5).

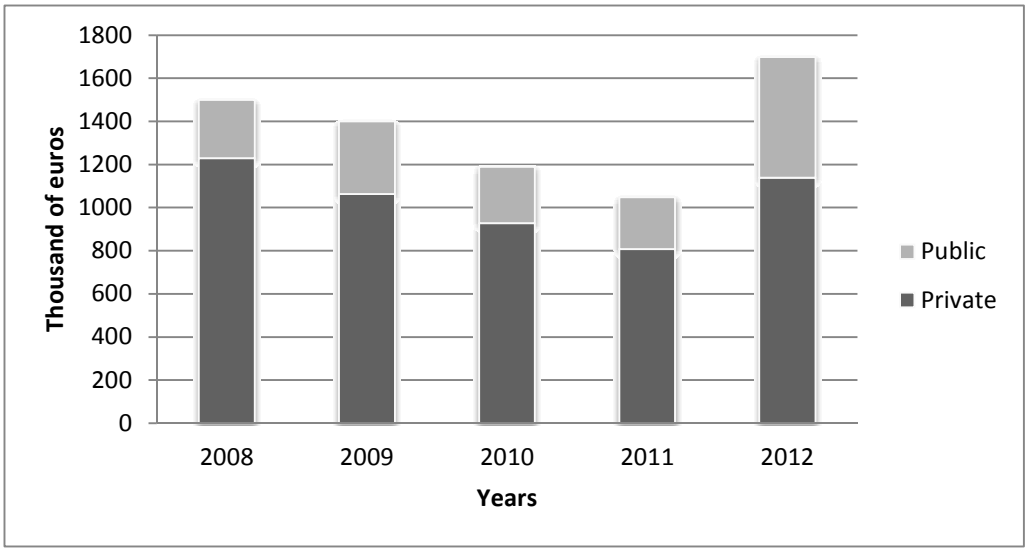

Figure 2 – Evolution of AIBILI funding in the last five years (5).

Regarding human resources, AIBILI has a permanent staff of 42 individuals including medical doctors, researchers, engineers, pharmacologists, technicians, trial and project managers, study coordinators and administrative personnel. Another 64 individuals collaborate regularly on a part-time basis being involved mainly in research activities (1).

By the end of 2012, AIBILI counts 93 ongoing studies, services, projects and contracts from the different Research Centres. Between 2011 and 2012, 106 scientific articles were published (1).

AIBILI is certified by ISO 9001 for the following activities (1):

- Research and development in new technologies for medicine with particular emphasis in the areas of imaging, optics and light;
- Preclinical studies of new molecules of potential medical use;
- Performance of clinical trials;
- Planning, coordination, execution and monitoring of clinical research activities;
- Health technology assessment.

The main objectives of AIBILI are (3):

- To assume a leading role as an aCRO, supporting IDCTs, either at a national and international levels;
- To coordinate and promote the EVICR.net;
- To launch in the market innovative diagnostic products in ophthalmology;

- To maintain the Quality Management System and meet the requirements specified in the implemented standards;
- To assure a sustained growth based on solid financial conditions.

The main strategies of this aCRO are innovation and internationalization, assuming a leading role in translational research in vision and imaging and bringing together academic institutions and industry (1, 3).

The 4C Research Centre is an aCRO where I perform my internship. 4C supports the development and coordination of Investigator-Driven and Industry-Sponsored Clinical Trials by providing the services listed in

Table 3. This Research Centre has the support of the Champalimaud Foundation as the core unit of AIBILI for C-Tracer (Champalimaud Translational Centre for Eye Research) activities (6).

Table 3 – Services provided by 4C through a clinical research project's lifecycle (6).

Pre-Study Services	In-Study Services	Post-Study Services
Study Design	Study Management and Coordination	Data Analysis
Protocol Design	Monitoring/ Auditing	Final Study Reports
Informed Consent Form	Data Management	Regulatory Reports
SOP Development	Periodical Reports to the Sponsor and/or RA	Scientific Publication
Submissions to the RA	Pharmacovigilance	
Contracts Elaboration	Data Validation	

RA – Regulatory Authorities; SOP – Standard Operational Procedure

4C is currently staffed by an executive director, four medical consultants, six project/clinical trial managers, two information technology and one administrative assistant. The Medical Consultants involved in the Clinical Coordination of research projects are José Cunha-Vaz, Conceição Lobo, Rufino Silva and Joaquim Murta. The Figure 3 represents 4C organogram (1, 4).

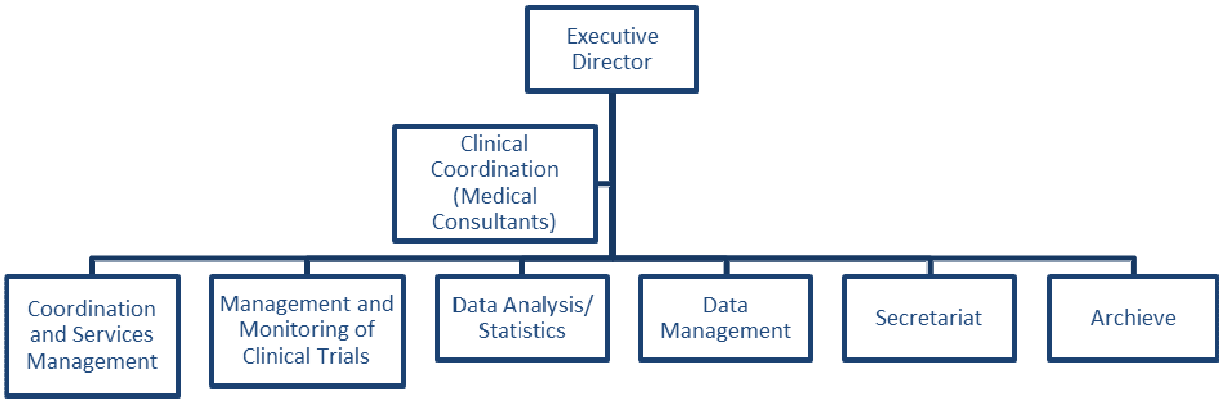

Figure 3 - Organizational flowchart of 4C (6).

Currently 4C is conducting 12 IDCTs and two Industry-Sponsored Clinical Trials. Table 4 specifies which of the studies that are undertaking are in a national or multinational (performed in at least two countries) level (1).

Table 4 – Current projects undertaking by 4C for clinical trial support (1).

Clinical Trial	Multinational	National
Investigator-Driven	RET-2010-02	Epidemiological study of AMD incidence
	EUROCONDOR	Life style and food habits in population aged >55
	C-Tracer Project nº 1	Macugen vs PRP in Proliferative Diabetic Retinopathy
	PROTEUS	Lucentis vs PRP in Proliferative Diabetic Retinopathy
	Vitamin D3 – Omega 3	DIAMARKER
		Diabetic Retinopathy Phenotypes
		Genotypes/ Phenotypes in Nonproliferative Diabetic Retinopathy
Industry-Sponsored	POLARIS	Pharmacokinetic assessment

AMD - Age-Related Macular Degeneration

1.2. Training objectives

The general objective of my curricular training was to consolidate the knowledge and tools acquired in the Biomedical Sciences Degree and the Master's Course in Pharmaceutical Medicine, through the experience gathered from working as a project manager assistant in an institution dedicated to the development and testing of new products or new therapeutic approach for medical therapy.

More specifically, the objectives that I established to manage my curricular internship were:

- Primary objectives:

- To develop an active participation as a project manager assistant through different activities and tasks carried out in an coordinating centre for clinical research;
- To obtain specific working tools and techniques through the application of the skills already acquired and with the experience of senior professionals;
- To acquire a multidisciplinary experience to develop pharmaceutical research activities that enables me to integrate the current labour market;
- To apply and complement the theoretical background acquired during the first year of my Master Course and Biomedical Sciences Degree.

- Secondary objectives:
  - To improve my social skills: communicate and transmit ideas, work as a team member, manage time by establishing priorities;
  - To improve my ability to analyse information critically and solve problems;
  - To gain autonomy in follow-up activities involved in an IDCT management;
  - To improve my medical writing skills by the support provided in the elaboration of study documents;
  - To demonstrate motivation and learning skills through the application of the knowledge gathered in 4C in my daily activities;
  - To acquire a comprehensive understanding of a clinical research project's lifecycle;
  - To know the main diagnostic ophthalmologic exams and the diseases - Age-Related Macular Degeneration (AMD) and diabetic retinopathy (DR) – and their pathological processes and current therapeutics;
  - To understand the multidisciplinary framework of a clinical research coordinating centre and the specificities of an IDCT;
  - To know the structure, function mode and the main activities carried out by AIBILI's Research Centres, with special emphasis on 4C.

1.3. State-of-the-Art

Clinical trials are mainly conducted by the pharmaceutical industry in order to generate data on the safety and efficacy of medicinal products they are developing. There is however an increasing interest by non-industry actors (academics, foundations, hospitals and research-networks) (7).

According to ICH-GCP, the sponsor is an individual, a company, an institution or organisation which takes responsibility for the initiation, management and/ or financing of a clinical trial (8). In IDCTs the sponsor is one investigator (sponsor-investigator) who both initiates and conducts the clinical study. This person is also responsible for the administration, dispense and usage of the investigational product to a trial subject (9). IDCTs are aimed at acquiring scientific knowledge and evidence to improve patient care. Such studies deal with potential diagnostic and therapeutic innovations that do not attract or could even be against commercial interest. They form a key part of patient-oriented clinical research and create the basis for continually improve patient care. Typical examples are proof-of-concept studies, studies on orphan diseases, comparison of diagnostic or therapeutic interventions, surgical therapies or novel indications for registered drugs (10). These trials provide the evidence needed for establishing treatment recommendations and ultimately guaranteeing the proper use of public healthcare resources. In addition, they speed up access to different treatments and maintain leadership and competitiveness by constantly encourage the design and conduction of more clinical research (10).

From the perspective of the pharmaceutical company, the central aim of supporting IDCTs is to collect additional safety data and information that could be used to support new indications or be included as part of the dossier for licensure. Investigator's interest in translational science dovetails with industry's desire to bring new products to market. IDCTs usually have greater interest in niche indications rather than company-sponsored ones which focus on the commercialization at large markets. Conclusions obtained from independent research might be hypothesis-generating while pharmaceutical industry focus medicine's licensing on safety rather than efficacy (especially if the product is only marginally efficacious). Concerning the conduction of an IDCT, the companies that provide the medicine must oversee the safety aspects and review any publications. Additionally, the compliance with ICH-GCP and suitable of capacities, facilities and procedures must be verified in technical and scientific standpoints. In addition the company has access to a complete safety database where the quality output is ensured (11). Table 5 highlights some key differences between IDCTs and company-sponsored trials (11).

Table 5 – Differentiating aspects of typical IDCTs and company-sponsored trials. Adapted from **(11)**

Aspects	IDCT	Company-sponsored trial
Primary purpose	Scientific research intended to publication or search for additional funding. To compare efficacy of drugs from different marketing authorisation holders.	Regulatory submission of a product intended to large markets In order to generate financial outcomes.
Funding Mechanism	Different departments in a pharmaceutical company.	R&D budgets inside the company.
Study Conduct	Conduction of the clinical study must follow ICH-GCP, regulatory and quality guidelines.	The clinical study must follow regulatory guidelines, company SOPs and ICH-GCP.

SOP – Standard Operational Procedure

With the demand to bring innovative therapeutics to patients many companies realised that they need to look beyond their own walls for innovation (12). The increasing in R&D investment, drug failures and patents expirations are driving pharmaceutical companies to seek a new collaborative model to stimulate innovation. The idea that the next new approach might not come from internal research has led many companies to shift their R&D expenditures externally through collaborations with academia. Companies start to seek the knowledge where it is generated – through contribute of independent investigators (12). An important aim for both types of organisations is to close the gap between basic and clinical research, thereby allowing for a more evidence and outcomes-based approach to therapeutic development. Such approach will allow collaborative teams to work together to identify what the innovation gaps are in the development of new therapies, what needs to be accomplished and whose contributions are more valuable (12). In addition, Academic Medical Centres (AMCs), including both health sciences schools and health systems are important partners in clinical research (12). AMCs train future generations of physicians, pharmacists, nurses and other professionals that contribute to the whole clinical research project's lifecycle.

Pharmaceuticals companies may provide support to investigators through various mechanisms (giving financial support, providing study medication). The clinical researcher, as the sponsor-investigator, assumes responsibility for designing the study; writing the protocol; monitoring the study; managing, analyzing and reporting the data; indemnifying investigators and trial subjects and selecting study personnel. In this context, clinical coordinating centres, acting as CROs, support the sponsor-investigator in all this clinical tasks (11, 12). Table 6 presents industry – investigator relationship models, its advantages and disadvantages, based on interviews with some of the leading life-sciences companies and the academic and non-academic researchers with whom they work (12).

Table 6 – Principal models for industry-investigator partnerships. Reproduced with authorisation **(12).**

Model	Definition	Advantages	Innovation disadvantages
One company – one investigator	A company forms a relationship with an investigator by providing funding for research.	Provides a starting point for establishing a productive relationship.	Does not explicitly encourage and often restricts communication with other investigators or companies that might bring value to the research; dilution of research effort.
One company – one university	A company develops a master agreement with a university and provides resources for a number of research projects with a single university.	Better leverage of an existing relationship; master agreements streamline process of initiating new collaborations.	Might be limited to capabilities and expertise of a single university; working with one company might limit the scope of the research; university is seen as extension of the company.
One company supports a university consortium	A company builds a consortium of several universities that focus on a specific topic.	Universities share and leverage their joint knowledge and the company funds a broader scope of research.	Limited interaction with a single company will not address industry-wide obstacles.
One company supports a university institute	One or more companies give a large donation to fund an existing institute or to establish a new institute at a university.	The company has access to network of investigators and universities receive funding to support its research in a specific area.	Researchers are often asked to keep resources and information around a project proprietary.
Industry consortium (pre- or noncompetitive)	The consortia could be structured to include many companies with one AMC, or conceivably many companies with multiple AMCs.	Ability to effectively resource and address important but noncompetitive innovation challenges (for example, biomarkers).	Agenda might be dominated by individual company contributors and could erode perception of meritocracy; companies and AMCs will need to find ways to profit from their activities to sustain participation.
Competition	A company invests in multiple investigators to research the same topic; the team to achieve the goal first receives funds for the next phase.	The company engages multiple parties to focus on its problems.	Researchers cannot share resources or information with other universities; the team that finishes first might not be the best one to continue the project.
Venture capital investment	A company provides several experts with seed money to start a company; milestones are established.	May foster more rapid commercialization.	Researchers sever their academic ties, thereby forfeiting a major source of information and ideas.
Free-for-service	The university provides a unique service to the company.	Investigator can apply technology to real-world problems and receive funding; company has access to commercially unavailable technology.	The researchers feel like “hired help” rather than partners; defining the challenge limits the value the university can provide.

The IDCT activity is quite different in Portugal than in Europe. Considering the number of clinical trials registered in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database from 2004 to 2013 (Table 7) the percentage of IDCTs, besides being constant, remains over time much lower than the commercial ones. The EudraCT number must be attributed to all interventional clinical trials with at least with one site in the European Union (EU). It is included on all Clinical Trial Applications (CTAs) within the European Community. The database went into operation on 1st May 2004 and has been established in accordance with the Clinical Trial Directive 2001/20/EC (13). The statistics presented were taken from the database on 1st March 2013 (14, 15).

From 2004 to 2008 there was an increase in the number of CTAs with a maximum of 9334 EudraCt numbers issued in 2008. In 2009, there was a significant decrease of EudraCT numbers issued, reaching up then a relatively constant number in the following years. Besides of these variations, the percentages of Investigator-Driven and industry-Sponsored Clinical Trials had sensibly remain the same over time (14, 15).

Table 7 – Number of EudraCT numbers issued per sponsor type, per year (14, 15).

Year		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013*
Total of EudraCT Number issued in		4613	6214	7214	7987	9334	6441	5914	6011	5399	981
Clinical Trials recorded by sponsor type (%)	Commercial		5096 **(82%)**	5844 (**81%**)	6390 (**80%**)	7420 (**79.5%**)	5089 (**79%**)	4672 (**79%**)	4749 (**79%**)	4265 (**79%**)	775 (**79%**)
	Non-commercial		1056 (**17%**)	1334 (**18.5%**)	1557 (**19.5%**)	1867 (**20%**)	1320 (**20.5%**)	1183 (**20%**)	1202 (**20%**)	1080 (**20%**)	196 (**20%**)
	Not indicated		62 (**1%**)	36 **(0.5%)**	40 (**0.5%**)	47 (**0.5%**)	32 (**0.5%**)	59 (**1%**)	60 (**1%**)	54 (**1%**)	10 (**1%**)

*Until 1st March

Considering IDCT at a national level, non-commercial research is more reduced. The percentage of non-commercial studies in Portuguese clinical research is less than 20% of the European average number of IDCTs. In Portugal, non-commercial sponsors accounts for 6% of the total number of CTAs to the National Authority of Medicines and Health Products (INFARMED). The highest number of IDCTs applications to INFARMED was 12, in 2009, of all 115 CTAs (16, 17).

The number of Clinical Trial Applications per sponsor type, from 2006 to 2012 is presented in Table 8. Once again, these statistics represent the number of interventional studies that are submitted to INFARMED (16, 17).

Table 8 – Number of valid CTAs submitted to INFARMED, per sponsor type, per year (16, 17).

Year		2005 (2nd semester)	2006	2007	2008	2009	2010	2011	2012	2013 (1st trimester)
Total number of CTAs		80	153	132	146	115	107	88	118	33
Clinical Trials recorded by sponsor type (%)	**Commercial**	76 (**95%**)	145 (**95%**)	127 (**96%**)	139 (**95%**)	103 (**90%**)	101 (**94%**)	82 (**93**%)	112 (**95%**)	29 (**88%**)
	Non-Commercial	4 (**5%**)	8 (**5%**)	5 (**4%**)	7 (**5%**)	12 (**10%**)	6 (**6%**)	6 (**7%**)	6 (**5%**)	4 (**12%**)

In 2009, the European Medical Research Councils of the European Science Foundation analysed the problems and needs faced by independent investigators when conducting IDCTs. For that, a series of workshops covering different themes and attended by active and acknowledged experts in the field was carried. As a result a report was produced, Forward Look – IDCTs (10). This document identified specific issues that need to be addressed and recommend a range of possible solutions. Similarly, in 2011 the OECD Global Science Forum launched, at the initiative of the German and Spanish Delegations a "Working Group to Facilitate International Co-operation in Non-Commercial Clinical Trials". This policy report also identified the main difficulties encountered by clinical researchers in setting up internationals clinical trials. Furthermore, they have recommended a series of policy recommendations aimed at overcoming the main difficulties faced in the process (10, 18).

Based on these two reflection reports and the experience that I acquired contributing to the conduction of national and international IDCTs, a description of the main hurdles in conducting IDCTs are presented.

Translational research is a powerful process that drives the clinical research engine. A strong clinical research infrastructure (comprising research centres and clinical trial units) is necessary to strengthen and accelerate the clinical research enterprise. These are centres of competence and excellence that are founded upon expertise and which provide access to patient-oriented research projects originating from the surrounding scientific community – academic, investigators or industry sponsors. The major need to perform high-quality investigator-driven clinical research is access to an infrastructure that functions as an aCRO offering centralized services and support, at affordable costs. This is particularly true when performing both multinational and multicentre

clinical research bringing together clinical research sites from different sites, with different requirements. Throughout the world, this type of infrastructure has been created in conjunction with AMCs. However, it may not be accessible to all sponsors of academic trials (4, 18).

In addition, existing infrastructures may have limited capacity to deal with international clinical trials. In Europe there is a lack of such infrastructure for clinical and translational medicine. Like infrastructures, the number of available well-trained investigators, who are capable of working together and with other clinical trial professionals, is often lacking. In many cases young investigators are not being sufficiently well trained to cope with the actual multidisciplinary environment. Furthermore, investigators have little "protected time" from clinical duties to perform clinical research – there is simply too little time available to pursue research. There is a lack of job security and a clear, well-defined and predictable career path for clinical investigators. Participation in research usually does not bring a competitive salary, which contributes to uncertain future prospects. Academic freedom appears to be diminishing with researchers being constrained by regulations and guidelines, which leaves less opportunity for imaginative, innovative research (1, 18).

It is very expensive to perform large-scale clinical trials. For this reason, large-scale clinical trials are mainly undertaken by the pharmaceutical industry for diseases that affect large numbers of people. Rare diseases groups or new indications for established groups are generally ignored. By the same token, funding for IDCTs was and frequently is lacking, even though such trials are capable of increasing basic understanding of diseases and improving healthcare. More public funding is required for academic clinical and translational research. The financial resources needed for national and especially for multinational European trials need to be secured. Funding should also be provided for both clinical investigators – to incentive the development of their careers – and specific infrastructures – to create optimal long-term clinical research. Such funding should be based on competitive peer-review and scientific and clinical excellence. This will assure that funding mechanisms for IDCTs will be coherent, instead of being heterogeneous and different between research's fields (10, 18).

The Clinical Trial Directive has brought about important improvements in the safety and ethical soundness of clinical trials in the EU and in the reliability of clinical trials data. However, the Clinical Trial Directive is arguably the most heavily criticised piece of EU-legislation in the area of clinical research. This criticism is voiced by all stakeholders – patients, industry and clinical investigators since (19):

- The number of applications for clinical trials fell by 25% from 2007 to 2011;
- Increase of costs to conduct clinical trials – to handle clinical trials authorisation processes, the cost of staff needs have doubled. In the case clinical investigators, the increase in administrative requirements has led to 98% increase in administrative costs. In addition, since implementation of the Clinical Trial Directive, insurance fees have increased by 800% for industry sponsors.
- The average delay for launching a clinical trial has increased by 90%.

The actual Clinical Trial Directive has hampered the setting up and management of non-commercial trials, particularly by the adoption of a "one-fits-all" national approach. In Europe, the same regulations that apply to higher-risk clinical trials of investigational medicinal products (IMPs) have been applied to all trials, regardless the risk involved and the objective of the trial. As a result, the requirements for low-risk trials, using already licensed drugs for similar indications, can be prohibitively onerous and time-consuming for academic institutions. In addition, the rules and regulations that govern clinical research are interpreted differently by the national and ethics committees' authorities from different countries. Adding this to the lack of appropriate infrastructure, funding and administrative support previously mentioned, the opportunity to conduct clinical trials by investigators are limited. The three obstacles that constitute urgent challenges to be overcome by clinical research teams wishing to undertake international clinical trials are (10, 18):

- Knowing about and understanding the existing laws and regulations, which can differ widely among countries;
- Filling in the submission dossiers and defining the assessment procedures required by all the national competent authorities involved in international trials;
- Answering to the different requirements of the numerous ethics committees involved in multi-centre studies.

There is a need to make a distinction between studies whose risk is equivalent to standard (usual) care (including randomised trials that compare already marketed and labelled treatments) and those that are aimed at innovation (testing a new drug or medical device). The current classification of trials does not make this distinction and has similar requirements for all categories of interventional trials. An harmonised regulatory approach to clinical trials based on

risk needs to be developed and the requirements of different types of clinical trials need to be reviewed (10).

With all the inconsistencies previously mentioned, launching and managing complex clinical trials, particularly at the international level, often remain a challenge for academic researchers. Approximately 24% of all clinical trials applied for in the EU are multinational studies. While these seem a relatively small proportion, this percentage of clinical trials involves approximately 67% of all subjects enrolled in a clinical trial. This means that, on average, a clinical trial with more than 40 subjects is conducted in more than one Member State. Mono-national trials are limited to small studies with low recruitment targets (18, 19).

2. Generic Training

The generic training provided by AIBILI allowed me to be familiarized with the activities of the institution and more specifically with the tasks of 4C.

Since the area of expertise of AIBILI is ophthalmology, most of ongoing clinical studies are on specific eye diseases. Likewise, this was the clinical area that I was involved in my training and the basis of my generic experience. The knowledge acquired gave me has a better understanding of some pathological processes that occurs in the eye as well as some diagnostic and treatment procedures that are executed in ophthalmological clinical trials.

A description of my training sessions, workshops and training course will be presented, according to the chronological order of occurrence.

Training Session on Ophthalmologic Procedures

The first training session that I had the opportunity to attend was on 14th November 2012, under the subject of "Ophthalmologic procedures: methodology and support in diagnostic". The session lasted three hours and was organised by the technical team of the clinical trial Research Centre (CEC) at AIBILI. This team responsible for the diagnostic procedures in the clinical studies is composed by 4 orthoptists: Pedro Melo, Ana Rita Santos, Mário Soares and Sílvia Simão.

The program of this learning session was:

- Definition of orthoptic;
- Areas of expertise and competence;
- Complementary exams in AIBILI;
    - Methodology and objectives;
    - Diagnostic support and treatment.

This training was of major importance for me in order to understand the different ophthalmologic diagnostic exams performed in AIBILI. Specifically, I became more aware of the different equipment used, their principles of functioning, the techniques undertaken to perform the exams, their applications in the clinical practice and their outcomes.

With this knowledge I could understand specific techniques and procedures mentioned in clinical studies protocols, as well as some requirements of inclusion and exclusion criteria.

Workshop: Investigator-Driven Clinical Trials – Relevance of New Structures in Portugal

This workshop was held in the Institute of Biomedical Research in Light and Image (IBILI) of the Faculty of Medicine – University of Coimbra on 16th November 2012, with two and half hours of duration. It was a workshop organised by 4C with open access to the general public, with the financial support of Bayer. The orators were José Cunha-Vaz (AIBILI), Rufino Silva (Coimbra Hospital and University Centre –CHUC/ CEC-AIBILI), Hugo Prazeres (Portuguese Institute for Oncology – IPO - Coimbra), Sandrina Nunes (4C-AIBILI), Cecília Martinho (EVICR.net), Pedro Caetano (*Universidade NOVA de Lisboa*), Ana Pais (*Universidade NOVA de Lisboa*) and Ana Isabel Severiano (INFARMED).

In this session various topics were approached, namely:

- Different perspectives on the conduction of clinical trials in Portugal by investigators from AIBILI, CHUC and IPO;
- The logistic and organisational support provided by 4C to investigators in clinical research;
- European Thematic Network - EVICR.net;
- Portuguese Clinical Research Infrastructure Network (PtCRIN);
- Clinical Trial Portal – PNEC.

With this workshop I became more aware of the difficulties faced by independent investigators that pretend to conduct clinical research in Portugal. Also, a new concept was introduced for me, the concept of aCRO. The existence of these structures is of major importance for investigators. They support all related trial-activities that need to be perform in order to implement a clinical trial.

The European Clinical Research Infrastructures Network (ECRIN) has been established as a not-for-profit infrastructure to support multinational clinical research projects. It started in 2004 with the first project on identifying the main bottlenecks to multinational cooperation in clinical research. This led to evidence of discrepancies in national organisation and practice of clinical research. As a result, ECRIN aimed to define a pan-European infrastructure for clinical research, based on the connection of national hubs providing services to multinational clinical studies. These national infrastructures provide services to investigators and sponsors in the conduct of multinational studies (20).

In a national scenario PtCRIN (ECRIN's member) aims to develop and to organise clinical research infrastructures, promoting its linkage and collaboration. This organisation concentrates efforts to

boost the productivity of all clinical research in Portugal, yielding a significant output of therapeutic innovation.

This training session also proportionated me a more comprehensive knowledge of 4C's scope of work and EVICR.net structure, objectives and ongoing studies.

Workshop: New Technologies for Medical -Imaging

This workshop was held in the IBILI's auditorium of the Faculty of Medicine – University of Coimbra on 30th November 2012, with two hours of duration. It was organised by CNTM and the orators were from CNTM – AIBILI: Rui Bernardes, Pedro Rodrigues, Pedro Guimarães, Conceição Lobo and João Figueira. Various topics were approached, namely:

- Vascular network of the human macula from Optical Coherence Tomography (OCT);
- 3D blood vessels segmentation form OCT;
- Phenotype/genotype correlation in DR;
- Adelphic eyes in macular holes.

With this training I became more aware of the scope of work that is conducted in CNTM. I learned that fundus imaging is needed for early and accurate diagnosis, to guide initiation of therapy and to evaluate the response to therapy of retinal diseases.

Training Session on Good Clinical Practices - ICH-GCP Guidelines

This training session was held in AIBILI, on 17th December 2012 and organised by UGQ Structural Unit. It took a total of four hours and was lectured by Cecília Martinho, AIBILI's Chief Executive Officer (CEO). This was a very relevant training session because I could remind and consolidate some standards and concepts previously acquired during my academic education. Having knowledge on this international standard is of major importance because it states how clinical trials should be conducted; define roles and responsibilities of clinical trial sponsors, clinical research investigators and monitors. It assures that the human rights are protected during a trial and assures the efficacy and safety of new products.

Training Course in Ophthalmology – Age-related Macular Degeneration and Angiogenesis

This training course occurred in AIBILI, on 14th, 15th and 16th January, with a total of 15 hours of duration. It was organised by the physicians and technicians of CEC. The trainers were Inês Marques MD, Maria Luz Cachulo MD, Sérgio Leal MD, Isabel Pires MD, Luísa Ribeiro MD MSc, João

Figueira MD MSc, Rufino Silva MD PhD, Pedro Melo BSc, Ana Rita Santos MSc, Sílvia Simão BSc and Mário Soares BSc.

The main objectives were to present basic notions about the ocular's anatomy and physiology, the pathologies of the eye and the complementary exams used to access eye fundus pathologies. Also, the course aimed to understand angiogenic mechanisms, to review the more important AMD clinical trials and to know the most recent treatment used in AMD clinical practice. The topics approached were:

- Ocular anatomy and physiology. Clinical trials with anti-vascular endothelial growth factor;
- Pathophysiology of AMD;
- Complementary diagnostic procedures in AMD;
- Therapeutics in AMD;
- Main pathological processes in the eye;
- Angiogenesis;
- Therapeutics of exudative AMD.

This training course was of major importance because I could acquire a more comprehensive knowledge about the clinical areas of AIBILI's expertise. Also, I gained knowledge on the scientific background concerning AMD clinical trials that enables me to understand the current clinical practice for the treatment of this disease. This scientific information facilitated some of my activities during my curricular training, namely the elaboration of an Informed Consent Form (ICF) for a DR clinical study.

3. Specific Training

According to the ICH-GCP a CRO is a person or an organisation contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions (8). An aCRO also provides contract services to external commercial sponsors initiated studies in addition to support the design and conduct of investigator initiated studies. The task of development new products with smaller in-house staffs has led to pharmaceutical companies to increase their reliance with CROs. It is estimated that more than 60% of all clinical studies now involve significant outsourcing (21).

A CRO can provide all services to the client in relation to the research project design, implementation and conduction. The main functions required to carry out a research project which are usually the departments in a CRO are (22):

- Medical Function: personnel medically qualified who help the design of a clinical study, help to develop clinical trial protocols and provide medical related input throughout the study. This includes medical monitors, clinical research physicians (investigator) and medical advisors.
- Regulatory Submission: this department assists in submitting various documents and obtaining approvals from regulatory authorities. It is composed by a regulatory affairs person.
- Clinical Operations: this department is responsible for the conduction of the clinical research project (selection of clinical trial sites, conducts monitoring at sites, assists in study closeouts and helps in all study management). It consists of clinical research associates (CRAs), project managers, clinical trial assistants and project manager assistants.
- Data Management: this department designs tools and databases to collect data (Case Report forms – CRF and Electronic Case Report Forms - eCRF). It helps to ensure that the data collected from clinical trials is clean and ready for analysis. It is composed by data managers.
- Data Analysis and Statistics: department where study data are analysed according to the protocol. Biostatisticians help to generate statistical tables, figures and graphs and their interpretations are an input for the elaboration of the clinical study report.

- Medical Writing: Medical Writers help to write study-related documents (reports, study protocols, promotional material).

As a project manager assistant, I had the opportunity to participate in different research activities, through different development stages of 11 clinical projects (Table 9 and Table 10). This experience gave me a broader vision of a clinical project's life cycle.

Table 9 – Participation in Clinical Research Projects during my curricular internship.

Study Acronym	Purpose	Sponsor	Design
CEC-120	To assess Genotypes/Phenotypes correlations in type-2 DR	IDCT	Observational study
Epidemiological	To assess the prevalence of AMD in the Portuguese population with age greater than 55 years-old and to characterise patients with this disease.	IDCT	Observational study with a single visit
EUROCONDOR	To assess whether neuroprotective drugs administered topically are able to prevent or arrest neurodegeneration as well as the development and progression of DR in its early stage	IDCT	Multinational, prospective, phase II-III, randomised controlled trial
LHON	Disease registry on LHON	Industry	Observational study
Life Style and Food Habits Questionnaire	To evaluate the frequency of nutritional and lifestyle risk factors whether separate and/ or joint have a major public health impact in terms of AMD	IDCT	Population of the Epidemiological study and are invited to respond a validated life style and food habits questionnaire
Lucentis CNV	To assess the efficacy and safety of Lucentis in patients with subfoveal and justafoveal choroidal neovascularization	IDCT	Multicentre, prospective, phase II, open-label
Lucentis RD	To assess the efficacy and safety of Lucentis in patients with high risk proliferative DR	IDCT	Multicentre, prospective, phase II, open-label
Macugen	To assess the efficacy and safety of Macugen in patients with high risk proliferative DR	IDCT	Multicentre, prospective, phase II, randomised controlled trial
PROTEUS	To assess the efficacy and safety of different treatment combination in subjects with high risk proliferative DR	IDCT	Multinational, prospective, phase II-III, randomised controlled trial
RET-2012-02	To identify progression of retinal disease in eyes with non-proliferative DR	IDCT	Observational study
STAR	To assess the safety and efficacy and tolerability of eye drops as a complementary treatment for Diabetic Macular Edema.	IDCT	Multicentre, prospective, phase II, randomised controlled trial

LHON – Leber's Hereditary Optic Nerve Disease

Table 10 - Activities performed in different clinical research projects during my curricular training.

Clinical Research Projects/ Activities developed	Pre-Study Phase		In-Study Activities						Post-Study Activities	
	Documents elaboration	eCRF planning and validation	Site Feasibility	Construction of Study Files	Study Management	Data Management	Data Entry	Data Validation	End of Study – related activities	Archive and Destruction of Clinical Trial Documentation
EUROCONDOR	X	X		X						
PROTEUS	X	X		X						
STAR	X									
Epidemiological					X					
Life Style and Food Habits Questionnaire				X	X	X				
Macugen				X			X	X	X	
Lucentis DR									X	
Lucentis CNV										X
LHON			X	X						
RET-2012-02						X				
CEC-120							X			

In order to describe my on-the-job training, I organised my activities according to its order of occurrence in a life cycle of a clinical project (pre-, in- and post-study activities -

Figure 4). Also there were some activities that were independent of a clinical project's stage of development, that are described as transversal activities (

Figure 4).

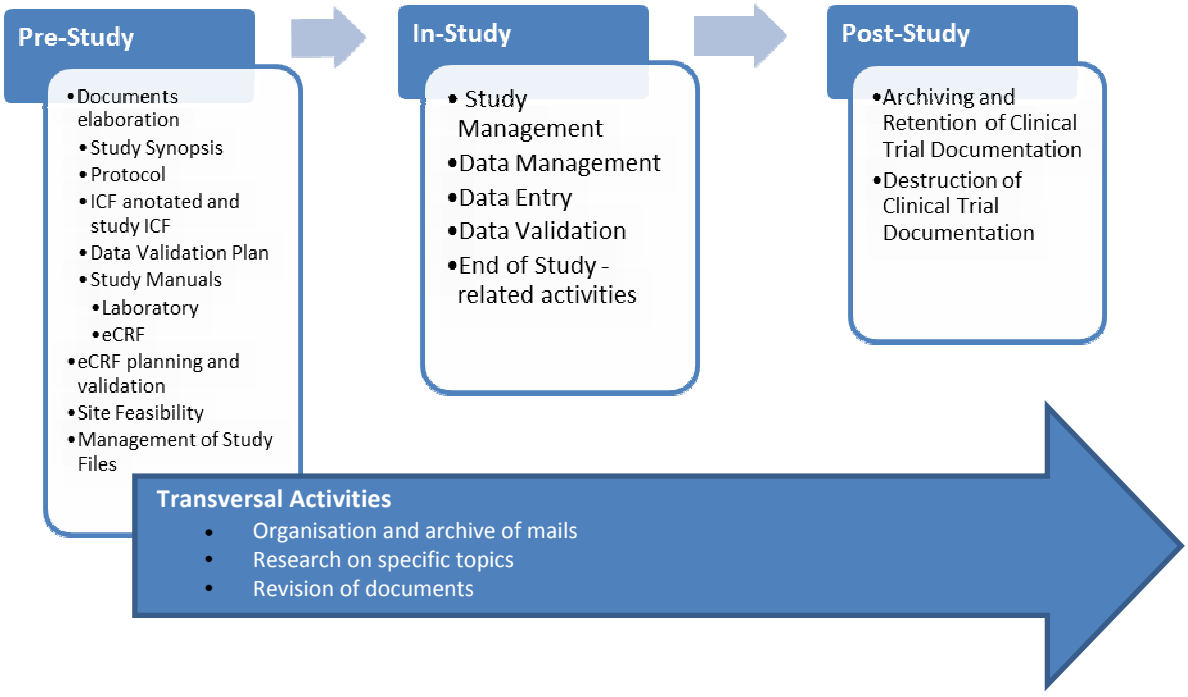

Figure 4 – Activities developed during my curricular training, according to its stage in a clinical research project development.

3.1. Pre-Study Activities of Clinical Trial

Before initiating the clinical phase of a research project certain activities must be carried out. Specifically the study must be designed, clinical study-specific documents elaborated (protocol, ICF, source documents), Standard Operational Procedures must be developed. In addition, submission activities to the regulatory authorities are performed and contracts elaborated.

3.1.1. Study Documents Elaboration

Study Synopsis and Clinical Trial Protocol

During my curricular training I had the opportunity to assist in the elaboration of a study synopsis and a clinical trial protocol. These were documents for the STAR and PROTEUS studies, two IDCTs on DR sponsored by AIBILI and EVICR.net and with the financial support of industry (Table 9).

The study synopsis is a short summary of the clinical trial. It is used to design and plan the study. This document is usually used to access internally the study feasibility at the scientific, logistic and funding level. The study protocol is the basis of a clinical trial. The protocol addresses the quality, the ethical feasibility and the objectives regarding the efficacy of the IMP. The responsible authorities can only give approval when the operations and methodology are described exactly and every step repeatable for another research team (23). The authorities provide the sections and organisation of the protocol. The main sections are (23):

- General information;
- Background information;
- Trial objectives and purpose;
- Trial design;
- Selection and withdrawal of the subjects;
- Treatment of subjects;
- Assessment of efficacy;
- Assessment of safety;
- Statistics;
- Direct access to source data/ documents;
- Quality control and quality assurance;
- Ethics;

- Data handling and record keeping;
- Financing and insurance;
- Publication policy;
- Supplements.

The PROTEUS protocol was elaborated from an AIBILI standard template designed to comply with regulatory requirements, ICH-GCP and AIBILI's policy. The project manager coordinate the different contributions in the protocol, namely from the coordinating investigator and the statistician. This document should meet the expectations and specifications defined by the coordinating investigator (24).

As a project manager assistant, my role at the elaboration of the study protocol was the implementation of some changes previously agreed and a final revision. In the process I could note the importance of team work - different people, with different roles in the institution contributing to the same outcome, the elaboration of a clinical trial protocol. For the study synopsis, I collaborate at the writing of the eligibility criteria, which was the similar from another study, with the same scientific background. This experience enabled me to gain a more specific knowledge about these two documents, with special emphasis on its structures and different function.

The Informed Consent Form

The ICF is the most important document for the protection of human subjects in clinical trials. During the trial, it also protects the sponsor from legal consequences if the patient is harmed. On the other hand, the patient is instructed about all his rights and duties, as well as possible risks and foreseeable adverse events. It can be used as a contract between the sponsor and the participant (25).

The ICF consists of two documents: the information sheet and the consent form. They are usually considered as a pair of documents and not as separate ones. The ICF template contains a core information that applies to clinical trial specific information and information that may need to be updated according to the specific local requirements (24). 4C has two templates, one in English for multinational studies and a second in Portuguese for national studies.

Concerning the ICF elaboration, I performed two activities: elaboration of an annotated ICF and an ICF for the PROTEUS clinical study.

For the elaboration of the annotated ICF, I introduced in the ICF template the specific requirements listed in ICH-GCP on the appropriate sections. This document serves as a "guide", with specific explanations for its realisation, always complying with the current regulatory requisites.

The PROTEUS study is a multinational study (Table 9) so the ICF has to be translated to the participating clinical sites, in different countries, according to their realities. For the elaboration of the ICF for this study I include the following information (25):

- Explanation that the clinical trial is part of research;
- Treatment during the trial;
- Probability for randomized allocation to a study group;
- Course of events and study design;
- Rights and duties of participants;
- Experimental aspects of the trial;
- Foreseeable risks for participants as well as for embryo, foetus and nursed infants;
- Expected benefits and the purpose of the trial; if there is no clinical objective expected the participant has to know as well;
- Alternative treatments for the participant and their side effects;
- Compensation and insurances for the participant if he/she is harmed;
- Expense allowance and possible personal expenses for the participant;
- Voluntary participation and possibilities for refusal at any time;
- Open access for responsible monitors, auditors, Ethics Committees, health authorities to every medical document regarding the trial including original documents;
- Data protection;
- Preservation of anonymity;
- Update changes of the trial for patients;
- Contact person or institutions in case of harm;
- Circumstances and reasons that can stop the participation or study;
- Expected duration,
- Approximate number of participants.

3.1.2. Electronic Case Report Form Design

The CRF is a printed or electronic document that is created and used in clinical research to capture protocol required clinical data from each patient and to transfer it to data Management (26). It enables data to be typed directly into fields using a computer and transmitted electronically to Study Database. A well designed and properly structured eCRF is a prerequisite for simplified data collection and for minimisation of data entry errors. eCRF design technique in terms of eCRF layout, organising eCRF modules with comprehensive eCRF completion instructions are all necessities for its success (27, 28).

Aligned and structured CRF fields provide a clear direction for data collection and for annotating eCRF and should always be organised in accordance with the protocol visits schedule. For example, demographic data and informed consent are always the first data collection modules in a eCRF followed up by the physical and laboratory assessments (28).

The definition of the parameters to be collected such as the nature of the variable (scale, nominal or ordinal), the number of decimal units are critical issues for a well-designed eCRF, for example, pre-defined format for the laboratory units (Figure 5) (28).

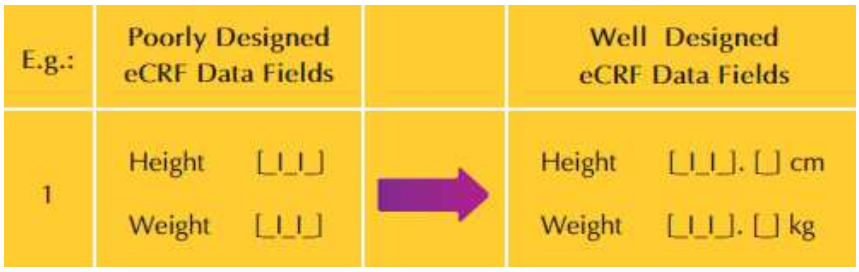

Figure 5 – Example of pre-defined formats for specific data units (28). eCRF – Electronic Case Report Form.

The classical CRF and Electronic Data Capture (EDC) construction is an interactive process involving professional for different specialties (data manager, database specialist, an EDC programmer) - Figure 6 (29).

I participate in the collection of all variables needed to include on the eCRF to a single document. As for variables, their specifications and units were also included. This activity was for the initial design of the PROTEUS study eCRF. Planning the design of eCRF by structuring study variables and specifications ensure that the information mentioned in the protocol is respected. For this activity I have based some of my work in the variables of the EUROCONDOR study (an ongoing multinational study on DR - Table 9), since it has similar procedures.

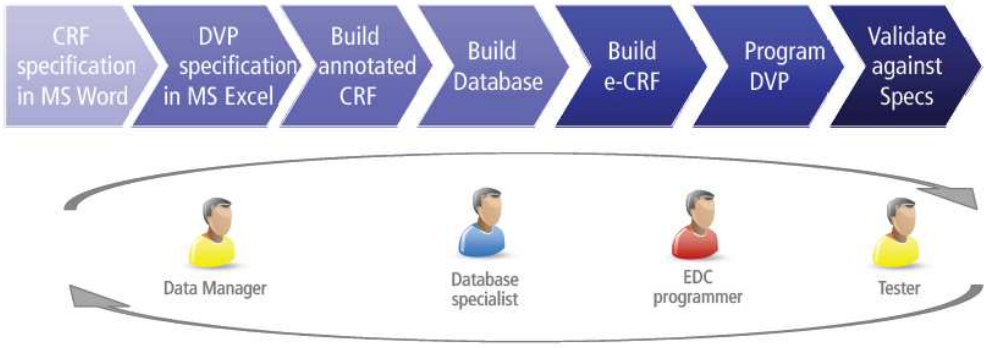

Figure 6 – Interactive process of setting up a CRF and EDC (29). MS – Microsoft; DVP – Data Validation Plan; CRF – Case Report Form; e-CRF – Electronic Case Report Form.

3.1.3. Data Management Plan and validation of an eCRF

The scope of data management is: to deliver a computerised system to support the tracking; to carry out data capture and data cleaning of collected patient data and to support the clinical team in setting up various documents, specifying how the above activities should be defined and supported (30). So, data management plan describes the activities to be conducted in order to ensure that data is collected, validated, completed and consistent.

The data validation plan is part of the data management plan. It describes either the automatic validation rules and electronic validation checks (automatic queries) being applied to the clinical data. Automatic data validation rules provide control for data accuracy. They are triggered during data entry, warning the user in real-time that invalid data is being saved. Electronic validation checks are used to fire a query message when discrepant data is entered. They help increasing the quality of the clinical trial data. Where data entered does not pass validation rules and/or the edit checks, and then a data query may be issued to the investigative site where the clinical trial is conducted to request clarification of the entry. Only the site staff with appropriate access may modify data entries (30).

In the elaboration of the data validation plan, I had the opportunity to assist in the description of the validation rules concerning the data entry in the EUROCONDOR eCRF.

As mentioned previously, I collaborated in the compilation of all the variables needed to be included in an eCRF of the PROTEUS study. It is a very preliminary activity for the eCRF development (Figure 6) (29). I had the opportunity to participate in another stage of eCRF

development. During the construction of the EUROCONDOR eCRF I could also assist the study project manager in the validation tests of the various fields, from different clinical trial visits. This process was executed with two different access logins – investigator and administrator. Each login/password combination is related to an access role that grants permissions to read and/or write only on the designated forms and perform certain tasks. In this activity, I deliberately introduce abnormal values that are expected to bring a query. Then it is verified if queries are raised. If not, I registered the fields that are not executing validation checks and inform the EUROCONDOR's project manager. It was an interactive process between me, the project manager and the entity outsourced responsible for the construction of the eCRF.

3.1.4. Study Procedures Manuals – electronic Case Report Form and Laboratory

Study procedures manual contains practical aspects of the study not included in the protocol. Two manuals that I had the opportunity to collaborate in their execution were the laboratory and the eCRF manuals, for the EUROCONDOR study. Being a multinational study, all these documents were posteriorly distributed to the participating sites, from different countries.

The laboratory manual included regional information from the different sites, namely the reference ranges for the different laboratory testing. In this process, my functions were to compile and to integrate in a database the different reference values for biochemical, urine and haematological testing from the different clinical sites. It was an interactive process since the clinical sites commonly do not send the reference ranges for all the required testing. I had to communicate to the project manager the missing values, which in his turn had requested the missing values to the clinical sites. All this were performed in order to obtain complete information for the elaboration of the laboratory manual, within the established deadlines. Once the information was completed, I could update the reference ranges in the right section of the laboratory manual.

The eCRF manual provides guidance to use the electronic data capture platform. Specifically in the EUROCONDOR study manual, I wrote the orientations for the completion of inclusion (baseline) and follow-up visits and the adverse event forms. After the elaboration of the eCRF manual a PowerPoint presentation was done in order to provide training to the CRAs of the different countries. I could assist in the elaboration of this presentation. Furthermore, I had the

opportunity to attend the training session provided by the project manager to all CRAs involved. It was teleconference training and occurred at 5th December 2012.

3.1.5. Clinical Trial Feasibility

Delays in study start-up and patient enrollment are major problems for cost overruns in clinical trials. A well-designed and executed feasibility study is crucial to overpass this problem. Using a feasibility questionnaire it is possible to assess whether a given study can be conducted in a given clinical site. Several aspects can be studied:

- Regulatory challenges;
- Available patient population;
- Required expertise;
- Available equipment.

During my curricular training I had the opportunity to participate in the process of selecting clinical sites for an observational study. It was a disease registry in patients with Leber's Hereditary Optic Neuropathy (LHON), a rare disease that attempt to collect data of the patients that are followed at each clinical site (Table 9). It is a collaboration between Industry and EVICR.net.

Using a survey service-platform (Lime Survey), I was responsible to send the feasibility questionnaire to all the EVICR.net members sites (76 clinical sites from 16 European countries). For that, I constructed the questionnaire in Lime Survey after studying this tool. On the past feasibility assessments, the clinical sites received an email with the questionnaire in attachment. The study staff had to print it, respond to it on paper, scan and then send it by an email. This was the first activity using this online survey service. The activities involved on the study of Lime Survey will be described later.

After sending the feasibility questionnaire a reminder for the clinical sites was sent. The dates for sending the questionnaire and the reminder and its closure were previously agreed. During this process I followed-up the results to the questionnaire and compiled them in a single database for further analysis. In the agreed deadline there were few responses to the feasibility. Another measure had to be taken, specifically contacting the non-responders sites telephonically and

appealing for a response. I could assist the EVICR.net contact person in these calls. During this activity I contacted 4 clinical sites from Greece, Italy and Spain.

Other activity associated with this service was the feasibility reports to the sponsor. I also assisted in its elaboration, namely by providing information on the response status of all the clinical sites and in the text organization.

Lime Survey – an online survey service

As mentioned before, I was responsible for studying Lime Survey tool for further implementation in 4C and UGQ's activities. Besides the different contexts (clinical studies and quality management system) the tool can be equally used for sending and managing questionnaires. Initially another online survey service was studied – Monkey Survey. Different questionnaires were done under these two online programs (an already existing feasibility questionnaire and a questionnaire to evaluate client satisfaction). Then, I elaborate a comparative document concerning their characteristics on the survey construction (Apendix I), sending to participants and analysis of results. After discussing this conclusion with AIBILI's CEO, it was agreed that Lime Survey was a better practical choice.

Once chosen Lime Survey as the tool to send and manage questionnaires I elaborated a user manual for its main features (Appendix II). Also, it was agreed that I would provide a practical training session. It is schedule for 11th June and the attendees are UGQ and 4C's personnel. The training session will consist on the elaboration, sending an analysis of a feasibility questionnaire. At the end, the attendees will have to construct another questionnaire that will be revised and evaluated by me.

3.1.6. Management of Study Files

An important task assigned to me during my curricular training was the elaboration and management of study files. The organisation of Clinical Trial Documentation in 4C follows the ICH-GCP and the requirements specified in the AIBILI's Quality Manual (31).

The trial master file is the record for documentation and archiving of all accumulated study documents, particularly with regard to essential documents for conducting clinical trials. At the beginning of the trial, the sponsor and monitor are responsible for the documents stored in the trial master file. It is very important to keep study documentation organized in order to assure the

validity, quality and reliability of the obtained data. Thus, the organisation and handling in the trial master file assumes an essential role, particularly when the data may be inspected by the health authority or other competent authorities (32).

Since AIBILI is the sponsor of many IDCTs supported by 4C, trial master file are established, organized and storage at 4C facilities. The structure of investigator and trial master files are established according to the AIBILI's quality policy (33, 34). Additionally to the trial master file, for the EUROCONDOR study were also established trial master files site specific, containing specific information of each clinical site, in different countries.

The following list is according to ICH-GCP and represents the essential documents needed before the clinical phase of the trial starts (32):

- Investigator's brochure/Summary of Product Characteristics or other specific and current information about the IMP;
- Signed clinical trial protocol and amendments, as necessary, and the blank CRF design;
- ICF;
- Financing statements;
- Insurance statements;
- Signed contracts between the trial parties;
- Opinion and composition of the Independent Review Board;
- Any written information provided to study participants;
- Authorisation/approval/notification of the protocol by the health authority in compliance with the applicable regulatory requirements;
- Documents regarding the qualifications of the sponsor-investigator/subinvestigator(s) and other involved trial staff;
- Normal value(s) and range(s) for medical/laboratory/technical procedures and tests as well as the proof of competence of the procedure and/or test;
- Sample labeling of the IMP container(s);
- Instructions concerning the IMP an trial-related materials, in particular:
    - Handling (storage, packing, dispensing);

    - Distribution (distribution dates and method, batch numbers, tracking, condition review and accountability);
- Decoding procedures for blinded trials;
- The Master Randomization List;
- The Pre-Trial Monitoring Report/ Trial Initiation Monitoring Report, especially in case of multicenter trials.

I managed the trial master files for the EUROCONDOR, PROTEUS, LHON, MACUGEN, and Life style and food habits questionnaire.

An important part of the clinical trial files is its correct identification and logical organization in a harmonised way. This is very important in order to easily identify the clinical study and its content, tracking the information and allow a person exterior to the study to locate required documentation without problems.

The AIBILI's quality Manual specifies the requirements needed for the file's spine. The information that must be present is (31):

- Name "AIBILI";
- Name "4C";
- Service Identification: "Protocol Number/ Code/ Acronym";
- Service Intern Number;
- Dossier Identification (Master File, Investigator File);
- Sequential Number of Dossiers (Volume).

I was responsible to set up and update the spines of the dossiers as the clinical study occurred. I established and updated spines for all clinical studies carried out by 4C.

3.2. In-Study Activities of Clinical Trial

The conduction of the clinical phase of a research project is characterised by the execution of activities related to data management and coordination. Also, monitoring activities are performed in order to assure the quality of data generated through the clinical phase. Data management, data validation and pharmacovigilance activities are also other activities in this clinical phase. Periodical reports to the sponsor and Regulatory Authorities are also performed.

3.2.1. Study Management and Follow-Up Activities

The most frequent and time-consuming activity that I undertook was study management and coordination. The related activities on this topic were performed for two studies "Epidemiological Study on the prevalence of Age-Related Macular Degeneration in Portugal" and "Life style and Food Habits in population aged >55" (Table 9). These are studies are intimately related.

Epidemiological Study on the prevalence of Age-Related Macular Degeneration in Portugal

This study has the purpose to assess the prevalence of AMD in the Portuguese population with age greater than 55 years-old and to characterize the patients with this disease. The study has a single visit, performed at the primary health centres (Mira and Lousã). It consists in an interview to the participant and the acquisition of Color Fundus Photographs (CFPs) that will be graded by CORC. Subjects with probable diagnostic of AMD are referred to a Retina Visit in a Reference Hospital. If the patient is not followed-up in a reference hospital, they are scheduled for AIBILI medical observation.

Nowadays this study is close to the end of the clinical phase at Lousã. In order to reach the estimated number of patients needed for statistical analysis, the project manager had to adopt some tasks related to the study dissemination, which were assigned to me. It was decided that the coordinating centre has to contact the local radios in order to obtain a budget for the study advertising. Also, the parish centres need to be contact in order to obtain permission for the distribution of some study leaflets.

I contacted the radios S.Miguel 93.5 and S.André 100.5 requesting a budget for an advertising of 58 words. This promotion was previously elaborated by the project and study managers. After the telephonic contacts, I elaborated official letters to send the leaflets.

Furthermore, systematically I checked the correctness of the ICF data, namely if they were correctly signed and dated. If not, the principal investigator has to correct it.

Periodical Reports

With defined time spans, follow-up reports must be sending to the research team. In this context, a preliminary report was done with data from patients already included. Important information to be included were: number of patients included, patients already graded, % of retinal changes, % of Age-Related Maculopathy patients, % of wet AMD patients, % of Geographic atrophy patients, % DR patients and % of other changes. For the elaboration of this report I used an existent template and completed the required sections according to the protocol. The information about the study patients had to be adapted. I elaborated a consort chart to describe the study population at the time of the report. This scheme showed the number of all patients registered in the primary healthcare unit in Lousã. From this total, the patients contacted are organized according to whether or not the study visit was scheduled. Of the patients that do not have a scheduled visit, the reasons are presented and specified in numbers. From the scheduled participants, the number of attendees was also pointed. The preliminary report also included statistic data for demographic and potential risk factors for AMD. However I do not contribute for this part.

Apart for this preliminary report, the activity of study staff has to be closely monitored, namely the number of patients included and the exams graded by CORC. I assist in the elaboration of the periodical follow-up newsletters to the coordinating investigator, showing the inclusion status of patients.

An important activity that I contributed was the identification of patients included in the epidemiological study that are currently followed-up in CHUC. It is important to have this information in order to assess their medical history. For this, I crossed information from two databases and filled a medical file requisition form for all these patients. Once the medical files arrived at AIBILI, the study investigator could collect information to include in the study.

Life style and Food Habits in population aged >55

The study “Life style and Food Habits in population aged >55” is an extension of the “Epidemiological Study on the prevalence of Age-Related Macular Degeneration in Portugal”. The study consists in a single visit where subjects that participated in the Epidemiological study are

invited to answer a validated life style and food habits questionnaire, after signing a written ICF. At this study I assumed many activities.

Currently the study is taking place at the healthcare Unit of Lousã. The interviewers are voluntary students of "Escola Superior de Tecnologia da Saúde de Coimbra" attending the dietetics and nutrition course. During the study, I was responsible to invite telephonically the participants to answer the questionnaire in a specific weekly date, previously accorded with the dietitian students. Subjects that could not attend the visit, I re-scheduled them. The data collected during the visit were registered directly in the questionnaire. After the interviews, the project manager meets the students and received the completed questionnaires. Then I was responsible for the completeness and accuracy of the answers of the questionnaire. I checked questions not answered as well as crossed information in the questionnaires and ICF. In order to follow ICH-GCP, either ICF or questionnaires that have crossed information must be correctly signed and dated. When this requisite was not meet, I pointed out the specific document for further correction by the interviewers.

Alongside with this process, I elaborated and updated a database for the follow-up of participants. I registered the completed questionnaires by date of visit and participant identification data (number of participant and date of birth). Also the AMD diagnostic information from the epidemiologic study was assessed. These enable me to monitor the AMD disease status of completed questionnaires. Due to the need to have an equilibrated proportion of healthy and AMD diagnosed participants, I could control the scheduling of patients under these requirements.

In addition, the patients referred to AIBILI for ophthalmological observation were as well eligible to answer the food and lifestyle habits questionnaire. At this stage, I received training and acted as an interviewer. I was responsible to follow the visit dates of epidemiological participants and administered them the questionnaire. Each subject must have given written informed consent before the participation in the study. At this process I explained the objective of the study and the need to use the data obtained, always ensuring the participant confidentiality.

The study logistics were also under my responsibility. I filed the questionnaires and the ICFs in the respective master files, according to an increasing date of realization. I also managed the prints of these documents, in order to assure that the primary healthcare unit of Lousã has permanently an available stock. At the same time, I scanned the completed questionnaires for the dietitian students registered the data collected in an appropriate database.

3.2.2. Data Management

The workload in assembling clinical trial data for analysis is dictated by the quantity and the quality of data. Two essential features of data management are a validated computer system and a trained specialist staff.

The ECR-RET-2010-02 study is a multinational, observational study with the purpose of identifying eyes with DR that show worsening and retinal disease progression, in diabetic type 2 patients (Table 9). For that, non-invasive procedures have been taken through 4 visits. This study does not have an eCRF. Instead, designated investigator staff entered the information required by the protocol on to paper CRFs. Data from the paper CRFs will be entered by each site in the Study Data Worksheet, an excel data sheet, using single data entry. This worksheet was previously prepared by 4C and sent to the participating clinical sites, from different countries.

Each clinical site has to send to the coordinating centre monthly a copy of the Study Data Worksheet. Also, after a study discharge visit, a copy of the completed CRF has to be sent (by email or fax).

In 4C, under this study my activities were to support the process of completeness and accuracy of the CRF and the Study Data Worksheet entries. The coordinating centre has access to all relevant source documents. Thus, with this information I could confirm the consistency of source documents data with paper CRF entries and the adherence to inclusion/exclusion criteria. When abnormal values were encountered, study personnel were instructed to make the required corrections or additions. Where Study Data Worksheet data were absent, I registered the missing information on a site - personalised document. Afterwards I transmit to the main project manager this information: missing or abnormal values. In her turn, the project manager contacted the clinical sites to ask for further clarification on these values.

A follow-up of the monitoring process outcome were also performed. I updated the information contained in appropriate databases concerning missing data, study subjects visits dates and dates of the received CRF. The number of subjects under study, drop-outs, and screening failures was continuously followed-up.

At this study some incongruities has been found. Some clinical sites send the CRFs (on paper or email) and do not fill the Study Data Worksheet. In this cases I entry the data on the specific worksheet and scanned the CRFs. It must be pointed out that this study has no financial support and was the first IDCT sponsored by the EVICR.net.

3.2.3. Data Entry

Remote data entry is the process by which data are entered from the paper CRF into an electronic database (24). This is applicable only in the case of paper CRF retrieved from the sites to the sponsor. In this case, the database will need to be designed. The data structure should be laid out to be as consistent as possible with the other studies.

The Macugen study is a national prospective, randomized, open-label, phase II study (Table 9). In this study paper CRFs were used. As defined in the protocol, data from the CRFs were entered into the study database by 4C staff using single data entry. I follow this study at the end of its clinical phase. In this context, it was assigned to me the data entry activity. In the course of collecting and entering data in the database, errors were found. The process of correcting errors is called data cleaning. At this process I point out in the paper CRFs the discrepancies found and communicated them to the project manager. Also, when I was unable to read the entry information, the project manager was notified so that the entry could be clarified with the person who completed the CRF. Further clarification was sought.

With the queries clarified, the paper CRF was corrected and I introduce the new information in the database. I could also assist in the design of the database.

According to ICH-GCP, the sponsor should retain all of the sponsor-specific essential documents pertaining to the trial (8). Since the study had a single clinical site – CEC, AIBILI, I made copies of all CRFs. In this way, the sponsor could have records for this documentation for posterior archive.

The CEC/120 is an observational study to assess the genotypes/phenotypes correlations in type 2 DR (Table 9). For this study, 412 diabetic patients enrolled in a two-year prospective study (CPM study) were invited for genotype analysis. Specifically in this study I collected from the 412 patient's CRFs the values from BCVA at baseline (visit 1) and OCT exams from the 3 visits. For this task, due to the elevated number of CRFs, I collected the data in CEC, and introduce it in a proper database.

3.2.4. Data Validation

Data validation is the process of testing the validity of data in accordance with the protocol specifications. These databases are constructed according to the logic condition mentioned in the

data validation plan (previously mentioned in 3.1.3. Data Management Plan and validation of an eCRF).

Since the Macugen study does not have an eCRF, and the data entry process was remote, the validation process was also manually. With the help of the study manager, a second pass and verification step of all data entered was performed. The discrepancies between the first and second pass was resolved in a way that the data entered was a true reflection of the CRF content.

3.2.5. End of Clinical Study-Related Activities

As previously mentioned, I could follow the Macugen study when it was reaching the end of its clinical phase. At this stage, I could assist the study CRA in several activities.

First, INFARMED and *Comissão de Ética par Investigação Clínica* must be notified that the clinical trial ends its clinical phase. For that I fill the mail envelopes to be sent to the national ethic and regulatory authorities.

According to ICH-GCP, all clinical trial materials and IMP that have been used, partially used or unused but are no longer required for the study must be reconciled and disposed of appropriately (8). All IMP supplies need to be returned to the Sponsor or destroyed at the clinical site. This must be done with approval from the Sponsor and must be fully documented (8).

When IMP are returned to the Pharmacy department, IMP containers and their remaining contents for each clinical trial must be accounted for and documented in the Pharmacy file specific for that study. In the Macugen study I filled an "Investigational Product Return/ Destruction Form". In this document, the treatment units of the IMP for destruction/return were registered. Specifically, for each used or unused IMP, were specified the number of units, its batch number and the code breaking envelopes number. As agreed with the Sponsor (AIBILI) the clinical trial IMP was destructed on site (CEC). The unused IMP units (intravitreal injections of pegaptanib - Macugen) were disposed in a specific needles container. The remaining IMP package was disposed at the category-IV garbage container.

I performed a similar task for the study Lucentis RD. It is a national prospective, randomized, multicenter open-label phase I study and is still ongoing (Table 9). 4C, as the coordinating centre for the study, has make accountability checks and record the number of units that each clinical site receives. At this point, the CRA assigned me the filling of the "Investigational Product Return/

Destruction Form". This way is it possible to maintain an audit trail of study IMP dispensed for further analysis of unused and used medication units.

3.3. Post-Study Activities of Clinical Trial

Post-study activities of clinical trial concern the analysis of data with regard of the Final Study Report elaboration and posteriorly the scientific publication. Any required regulatory reports are addressed. Clinical trial-related documentation is archived and when applicable some documents are destructed.

3.3.1. Archiving and Retention of Clinical Trial Documentation

Archiving is the long term storage of all essential documents which individually and collectively permit the evaluation of the conduct of a clinical trial and the quality of the data produced (9). According to Article 17 of Directive 2005/28/EC, essential documents should be retained securely prior to archive and then retained for a specific period of time (35). Archiving of clinical trial data must be carried out in compliance with the Clinical Trial Directive, volume 10 of Eudralex – The Rules Governing Medicinal Products in the EU and ICH-GCP (35). Whilst the ICH-GCP do not explicitly define "archive" in the Glossary, they state that "all clinical trial information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification" (8).

Lucentis CNV was a national, prospective, multicenter, open-label study (Table 9) approved by the National Competent Authorities. Besides having a clinical trial authorisation the study was cancelled since the National Ethics Committee required conditions that were not feasible for an IDCT.

According to the ICH-GCP, if the Sponsor discontinues the clinical development of an investigational product, the Sponsor should maintain all Sponsor-specific essential documents for at least two years after the formal discontinuation or in conformance with the applicable regulatory requirement(s) (8). At this point my function was to prepare the archiving process of the study specific documents, following the instructions of the AIBILI's Internal Quality Manual. For that, I filled the "Submission of Material to the Archive" and the "Clinical Trial Archive Record"

forms. In these documents, the number of all sheets in the submitting files was counted. They were specified by chapters. The compiled study documentation was saved in appropriate dossiers, identified under specific instructions. These are counted and also registered in the forms previously mentioned.

In addition to the archive of the Lucentis CNV study, I also prepare the submission of another service carried by 4C. The service was named "ATRAL" and consisted in monitoring services of a phase I study carried out by CHAD. The CRA of this study was from 4C.

For this process the same forms were filled and the documentation were also organised as previously mentioned.

3.3.2. Destruction of Clinical Trial Documentation

I carried out the destruction of trial documentation of the Investigator Files for the Study Lucentis CNV that was cancelled. Since the study did not start, the investigator files were not distributed to the clinical sites. Thus, they do not possess any essential and site specific trial documentation (35). The common documents where destructed and the files re-used.

3.4. Transversal Activities of Clinical Trial

Transversal activities of clinical trial were independent of the clinical project's stage of development, and occurred whenever the work undertaken in 4C demanded.

3.4.1. Online Research Activities on Specific Topics

During my curricular training I performed many online research activities on many different topics. It has showed to be a great opportunity to strength the research tools gathered in the Biomedical Sciences Degree, from the problem based learning activities. Always looking for online reliable sources and criticising the data which the information was produced, I research the:

- Data validation plans;
- Elaboration of surveys in the programs Lime Survey and Monkey Survey;

- Statistical measures for inter-rater agreement;
- Parameters for clinical software validation;
- Summary of all clinical trials registered in the clinicaltrial.gov platform involving some medical products;
- Guidelines for the conduction of registries studies;
- Differences between personal data and study data;
- Description of the genes involved in the clinical study CPM/CEC/120.

I gathered as much relevant information as I could. Next the information were compiled and studied. As a final result I presented the document with the information summarized and explained the main ideas for the senior project manager who requested the activity.

3.4.2. Revision of Documents

Another activity that occurred with undefined time spans was the revision of different documents. In these activities I look for possible spelling errors and any discrepancies. The following documentation was subjected to revision by me:

- CHARTRES study synopsis;
- Quality General Procedure number 16, English and Portuguese versions. It is a procedure included in the Quality System Manual concerning the implementation, coordination and monitoring of clinical studies undertaken by 4C;
- "Logistic and organizational support needed – aCRO's" presentation, included in the workshop "IDCTs – Relevance of New Structures in Portugal";
- "Good Clinical Practices" presentation, for the workshop about ICH-GCP;
- "EUROCONDOR: eCRF Training" presentation, for the EUROCONDOR'S CRAs training session;
- Initiation visit presentation for the C-TRACER clinical study.

Most of these documentations were for oral presentations. Concerning the C-TRACER initiation visit, I also had the opportunity to attend it.

3.4.3. Organisation and Archive of emails

Organizing and archive emails correctly are a major requirement for the management and coordination of a clinical project. The trial master file and the studies files should be kept organized and actualized. Also, these files are eligible for inspection by the regulatory authorities at any time during and after the study is completed and submitted for product approval. It is therefore, paramount that these documents are filed in a way to make them immediately accessible for use by the study team and for regulatory inspection.

A project manager should ensure that this documentation is ready for auditing at all times and that the study team can locate and use the information in a timely manner. This is even more important in the context of multinational clinical trials, where the amount of correspondence is bigger and its organization is more difficult.

In this context, I assisted the project manager to achieve and organise correspondence in the clinical studies under their responsibilities. The studies were: EUROCONDOR, Lucentis RD, Lucentis CNV, Macugen and LHON. In this process I organised the emails from the most recent to the oldest. From this activity I learned that it is very important to keep every decisions and exchange of ideas written. Having a response written in an email is a proof of its occurrence and is crucial for the clinical project conduction.

4. Discussion

Work in a clinical research coordinating centre gave me the chance to have a broader vision of a clinical research project's lifecycle. According to models of industry- investigator partnerships described in Table 6, the the model "one company – one investigator" is the reality that I contacted during my training. Companies support financially investigators who could be supported by coordinating centres in all activities needed to design and conduct clinical research.

Being involved in 4C's activities has enabled me to contact with an unfamiliar reality in the clinical research environment – the one that is initiated by independent investigators.

Personal experience, skills and competences gathered

My curricular internship included generic and specific training components. The generic training consisted in two distinct training sessions on ophthalmologic procedures and ICH-GCPs, two workshops on the relevance of new structures that support IDCTs and new technologies for medical imaging and a training course on AMD and angiogenesis. The activities carried out in my specific training followed the whole clinical research project's lifecycle. I had the opportunity to assist in pre-, in- and post-study activities. In addition I perform several tasks that I consider in this report as transversal activities since it were independent of the stage of development of a clinical research project.

The generic training of my curricular internship has enabled me to be familiarized with the activities of AIBILI and more specifically with the tasks carried out by 4C. At the training course it was possible to me to integrate the steps occurred in an inflammatory process, since it was already addressed in the Degree of Biomedical Sciences. As an outcome of this training I acquired knowledge on the main diagnostic ophthalmologic exams and the diseases – AMD and DR, their pathological processes and current therapeutics.

I really appreciated the fact that these training meetings occurred in an initial phase of my internship since it had allowed to integrate this knowledge on the current activities held in 4C. With these information contextualized and clarified, interpreting clinical trial protocols, writing an ICF or even managing clinical data become easier.

With the specific training had the opportunity to develop personal skills and acquire competences as a clinical research professional needed to integrate the current labor market.

Working in a RTO was a very enriching experience. I could contact with different departments inside the same institution and understand their different roles in the development of a clinical research project. At AIBILI, I gathered a whole new vision of team work for clinical research projects design and conduction. I could assist the "birth" of clinical projects at 4C, the initial share of knowledge and seek for funding. At CEC, the clinical studies initiated by AIBILI are carried out. The ophthalmologic exams are graded by CORC during the conduct of the study. CHAD in its turn is responsible for pharmacovigilance tasks. The reality of AIBILI is a true example of team work that needs a coordinating centre to ensure the quality in the clinical research project's conduction.

The multidisciplinary environment of a clinical research coordinating centre showed to be a major advantage in my training. I accomplish to acquire professional competencies for the development of clinical research projects activities through different project's lifecycle stages. I could participate in several activities: study documents elaboration, planning and validation of an eCRF, data entry and data validation, feasibility assessment, study and data management and archive and management of clinical trial documentation. In addition I could also assist the study monitor in end of clinical trial-related activities.

As the professional competencies acquired, I highlight:

- Comprehensive knowledge of the activities developed by a clinical research coordinating centre, acting as an aCRO;
- Knowledge of the role of a project manager assistant in all research project's lifecycle activities;
- Knowledge of the particularities associated with IDCTs;
- Development of follow-up activities associated with observational IDCTs management;
- Knowledge on the elaboration of study-related documents, namely the study synopsis, study protocol, ICF, Data Validation Plan, Laboratory and eCRF manuals;
- Knowledge on the planning and validation of an eCRF;
- Autonomy in the elaboration and management of study-related files;
- Development of data entry, management and validation activities;
- Knowledge on site feasibility activities;

- Knowledge on archiving and destruction of clinical trial documentation;
- Development of solving-problems strategies;
- Development of my English skills, both written and spoken.

I could also develop some personal skills. I point out the following personal skills improved:

- Time management by establishment of priorities;
- Adaptation to a new professional context;
- Fulfilment of tasks in the deadlines established;
- Team spirit and sense of responsibility;
- Analyse information critically;
- When communicating ideas, adaptation of speech and its content according to the listener.

I would also like to point out another aspect that was mandatory for the conduction of my activities in 4C. The fact that 4C's team has a good work environment facilitated my integration into the team. The personnel that work in 4C has a very solid team spirit, where opinions are taken into account and mutual help are frequently asked. Besides my lack of professional experience, I always feel like belonging to an already established team. This was crucial to the success of my curricular training.

Difficulties faced during the performance of some activities and strategies implemented

Life Style and Food Habits in Population Aged >55

The first challenging activities that I would like to address is related to the study "Life Style and Food Habits in population aged >55". It was the study where I spent more time working, moreover is where I can identify most the challenging activities and to establish improvement strategies. For start, the process where I contact telephonically the subjects of the Epidemiological study and invite them to participate in the food habits and life style questionnaire was not easy. I must explain that they are being invited to respond a food habits questionnaire because they already had participated in the Epidemiological study. It was an independent study, but only these subjects were being included. As a result of the telephone contacts, the participants who arrived at primary health care unit of Lousã thought they were going to do new eye's exams, like the previously CFP in the Epidemiological study. The messages do not translate

correctly and they do not understand the correct objective of their visit to the health care centre, being unsatisfied with the situation and refusing answering the questionnaire. At this point I had to adopt a new strategy to invite the subjects to participate in the questionnaire. I wrote a "guideline" with the topics that were very important to mention in the conversation. Just before ending the phone call I remind the date and hour of the appointment with the dietitians and that during it they will not perform any exam, just answer food-related questions. After changing my strategy at the phone conversations, the study participants arrive at the health care centre understanding their role at this visit. It is necessary to take special attention to the fact that these participants are 55 or more years of age. I should adapt the speech and choose carefully simple words to transmit ideas.

In addition, it has been very important to understand if the persons that cannot schedule a specific day for the realisation of the questionnaire actually are interested in participating in another date or are really not interested. It happened that the subjects that asked to be re-schedule when contacted for another date showed to be not interested. Again the need to have a concise, objective and simple speech became crucial in order to optimise this process and save time. I started to asks specifically if they would like to participating in another visit date instead of the "I call you later for a re-scheduled date". Maintaining a complete and accurate database of the telephone contacts status showed to be crucial for saving time in the process of scheduling patients.

Other aspect related to the life style and food habit questionnaire that had proven to be challenging was the obtaining the signing ICF. When the participants of the Epidemiological study were referred to AIBILI for ophthalmological observation, I administered them the life style and food habits questionnaire. For this, first it must be obtained a written informed consent. In this process, the participants that could read the information provided, preferred that I explain to them its content. Again, with a careful speech with simple words I had been explaining the objective of the questionnaire, how it is constituted and ask for they authorisation by signing the ICF. At this point having the capacity to summarise the information was very important. I had to be sure that the participants understand what I was asking. This was a process that became easier over time and more ICF were explained.

Complying with ICH-GCP requirements shows to be a process present at each stage of the conduction of the life style and food habit questionnaire. When checking the completeness and accuracy of answers it was very important to check any crossed information that was not signed

and dated. Every time that happened I have been pointing it out in the questionnaires/ICFs for the dieticians posteriorly sign and date. These are aspects that are checked in any internal or external audit, and it must be rigorously verified. Over time become easier to identify inconsistencies in the questionnaires and ask for further revision/correction. It had been happening that the ICFs were incorrectly filled and remains necessary to be as rigorous as possible. It would be of greater value if the dieticians could have had a training session addressing the application of ICH-GCP into the administration of the life style and food habits questionnaire and the ICF at their initial training as interviewers.

By assisting the study manager coordinating the activity of the dieticians I could note how important is to motivate and have a motivated team. A project and study managers have an essential role in motivating and stimulating the clinical team in order to obtain the best outcomes possible.

LOHN Registry Feasibility Activity

Concerning clinical trial feasibility activities, the low response rate by the clinical sites associated in a short deadline imposed by the sponsor demonstrated to be a challenging task to overcome. In order to overcome this situation, it was adopted a strategy of contact the clinical sites telephonically. More specifically, it was asked to talk to the investigators and if not possible to their secretary. It was requested new emails contacts for sending the feasibility questionnaire that were posteriorly added to the Lime Survey list of contacts. The deadline established to the sponsor was adapted and it was received more responses and feedback from the clinical sites. An important “tip” that I could learn from this process is that for contacting clinical trial centres for feasibility purposes it is very important to send the questionnaire not only for the investigator but for his secretary or study coordinators as well. Due to the elevated number of emails that an investigator could receive, it is very important to communicate with a larger number of clinical professionals involved in a trial. Also, I would like to point out an aspect that during my curricular internship I note that is very important – keep all information organised and easily traceable. During the follow-up of the responses to the feasibility were very important to keep all information recorded in different versions documents, and not substitute with more recent information. This way it is possible to consult information at different time points.

The knowledge previously acquired during the Degree in Biomedical Sciences and Master in Pharmaceutical Medicine was reviewed and many topics became clearer. I could recognize that the structure and curricular units of this master course were essential to have a better

understanding of real-life activities developed within the implementation and coordination of a clinical research project.

However, when starting my curricular internship I came across a reality that was totally unfamiliar to me. The role of independent investigators in clinical research, their main difficulties faced when conducting clinical trials, possible sources of financing and relevant supporting infrastructures were all aspects that were not addressed in the Master Course.

I suggest that in the future more importance is given to these topics in the curricular units. I think it would be of greater value have the presence of independent investigators in the curricular units for the future editions, and hear their experiences and evidences on how is to conduct IDCTs in Portugal. The vision of who conducts non-commercial interest clinical research is also important for our academic education.

5. Conclusions

My training experience in a coordinating centre for clinical research allowed me to acquire a comprehensive understanding of a clinical research project's lifecycle. I could assist in many activities required to design, implement, conduct and coordinate clinical trials. The experience of working in an aCRO was very challenging in many aspects since I could contact with a reality that was unfamiliar to me – the clinical research initiated by independent investigators. All these factors contribute for me to grow as a clinical research professional.

This experience also allowed me to understand the central role of a project manager in the conduction of a clinical research project through its development stages. I understand that a project manager plays a pivotal role in a clinical dynamic environment, serving as an operational point person in the management of clinical studies. I could also understand that these professionals must have a strong scientific knowledge of project management and coordination and must possess solid problem-solving and leadership skills. They are crucial to motivate a clinical research team.

After completing this training, I feel that I have grown as a clinical research professional. I improved personal skills and acquire professional competencies that, otherwise without this training experience would not be possible. Additionally, I consider to have contributed to the improvement of some activities carried out by 4C and UGQ with the implementation of Lime Survey as tool to send and manage questionnaires.

I am motivated to continue to develop my clinical research career with the certain that, in the future I would like to work in this area.

I recognize that pharmaceutical medicine professionals may provide a very important contribution to any institution who wants to conduct clinical research. With a multidisciplinary background involving many clinical research subjects, I could integrate different knowledge in the daily-basis activities carried out during my training.

In order to conclude this report I consider that the objectives initially established for my training were fully met.

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Appendix I – Comparative Document between Survey Monkey and Lime Survey

ELABORAÇÃO DE QUESTIONÁRIOS:

SURVEYMONKEY E LIMESURVEY

(COMPARAÇÃO DOS PROGRAMAS)

DATA DA VERSÃO: 2012-11-01

Documento de revisão

Versão No.	Data	Descrição	Elaborado por	Revisto por
0	2012-11-01	Elaboração de questionários: SurveyMonkey e LimeSurvey. Comparação dos programas	Ana Rita Ribeiro	Sandrina Nunes

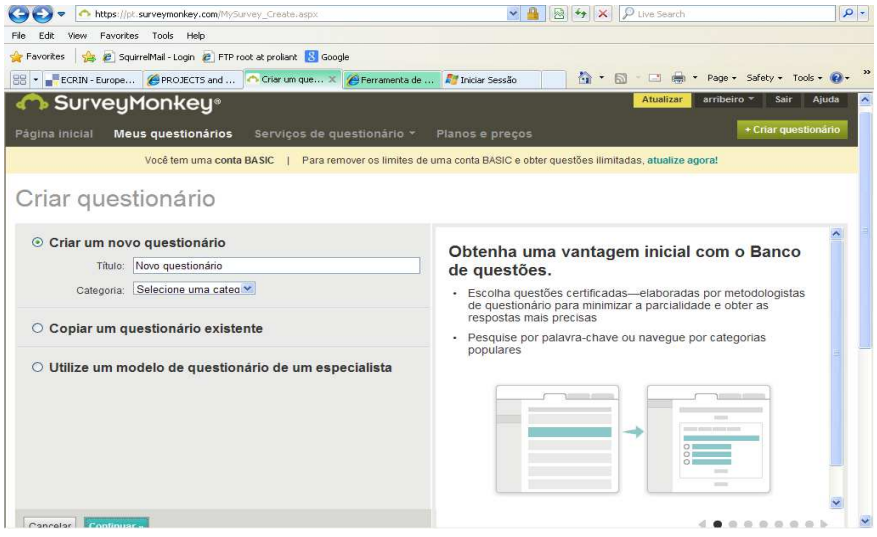
SurveyMonkey

Características

- Criação de questionários
    - 15 Tipos de questões
- Personalização dos questionários
    - Nome, cores, temas, logotipo da empresa (este último necessita de actualização do plano de preços)
- Gestão de repostas
    - Encerramento do questionário logo que alcançado o número de respostas desejado. É possível definir uma data e hora de corte, exigir uma senha e restringir as respostas a apenas uma por endereço IP
    - Incorporação do questionário no *site* da empresa
- Análise de resultados
    - Respostas recebidas em tempo real
    - Filtros de referência cruzada com os resultados
    - Exportação das respostas em múltiplos formatos (actualização de preços)

Construção de um questionário

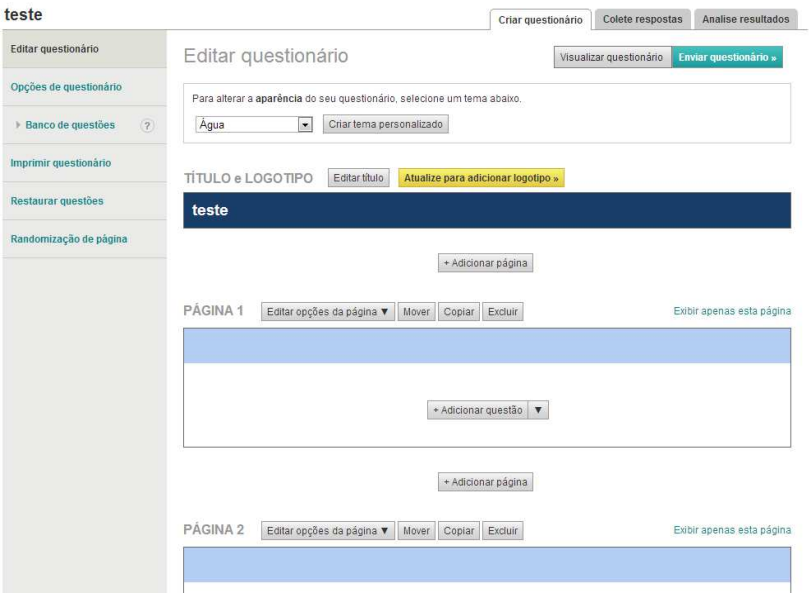
- Novo questionário (título + categoria)
- Utilizar um modelo de questionário
- Utilizar um questionário existente

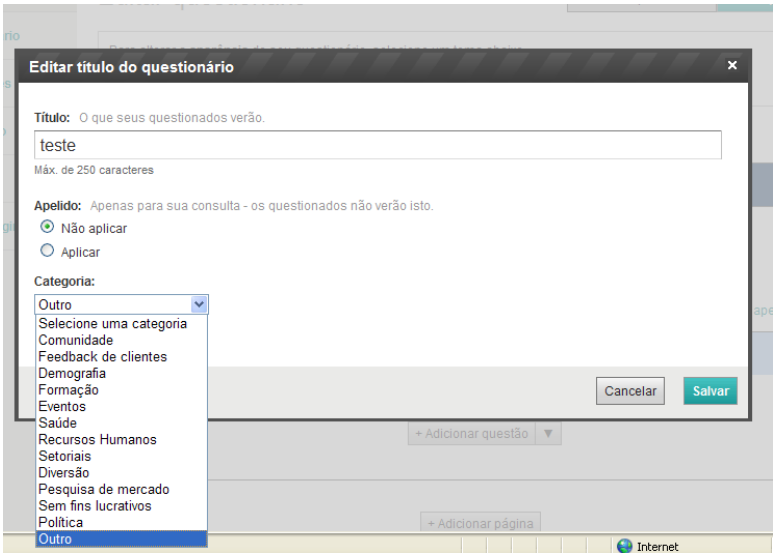


Edição do questionário (opções)

- Aparência

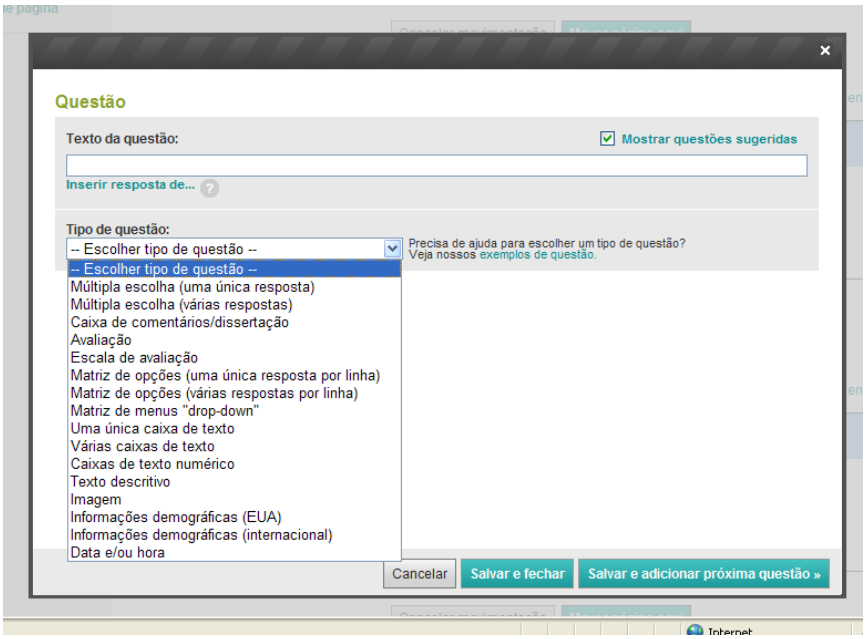
- Título e logotipo





- Páginas do questionário
  - Adição de novas páginas
  - Acrescentar randomização de página
  - Adicionar randomização de questão
  - Editar informação
    - Título da página (curto)
    - Breve descrição da finalidade da página
  - Adicionar questão
    - Texto

- Tipo

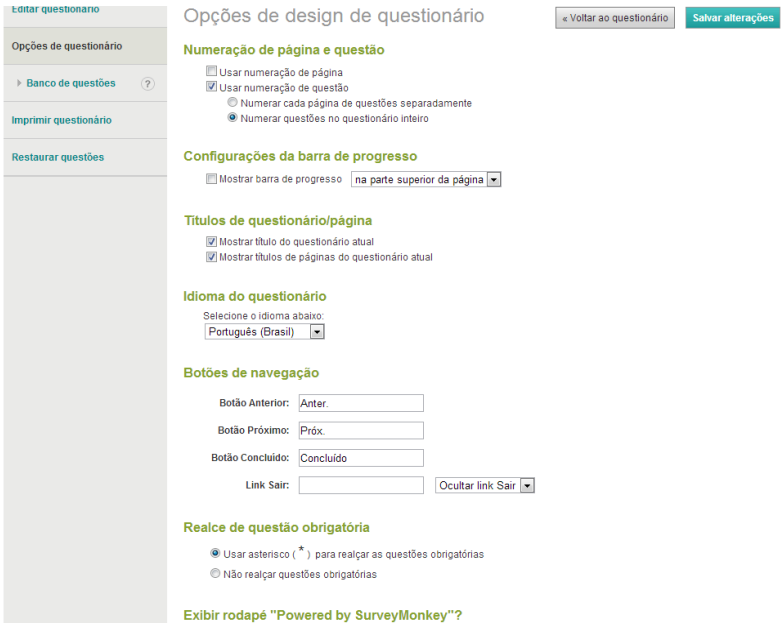


o Opções de Design do questionário (opções)

- Numeração da página e questão
- Configurações da barra de progresso
- Titulos de questionário/página
- Idioma
- Botões navegação
- Realce de questão obrigatória

Recursos GOLD

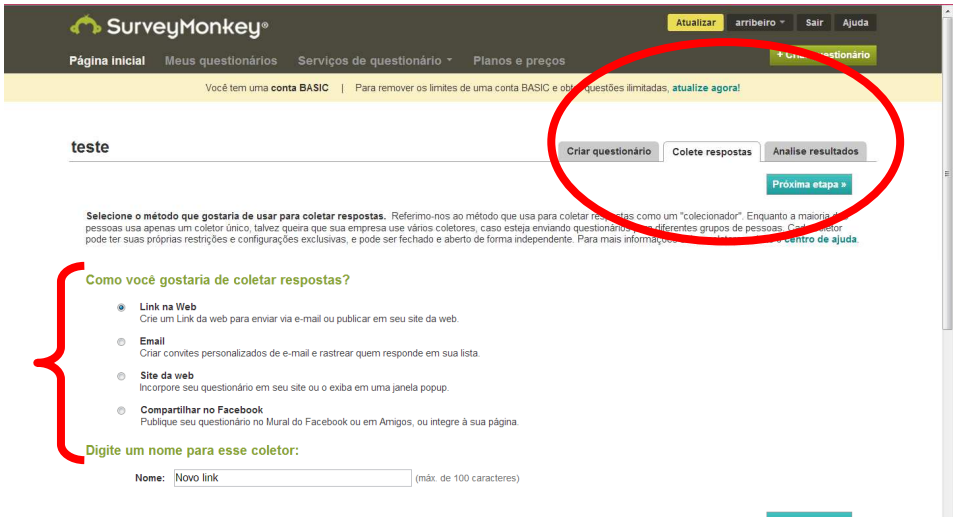
- Exibir rodapé “Powered by SurveyMonkey”
- Adicionar variáveis personalizadas (usar variáveis personalizadas para passar informações pré-coletadas ao questionário)
- Adicionar cotas ao questionário (usar cotas para definir limites referentes ao numero de respostas que poderão ser recebidas por questões especificas do questionário)



MAIS:

- Possibilidade de restaurar questões anteriormente eliminadas
- Banco de questões previamente formuladas

Divulgação do questionário

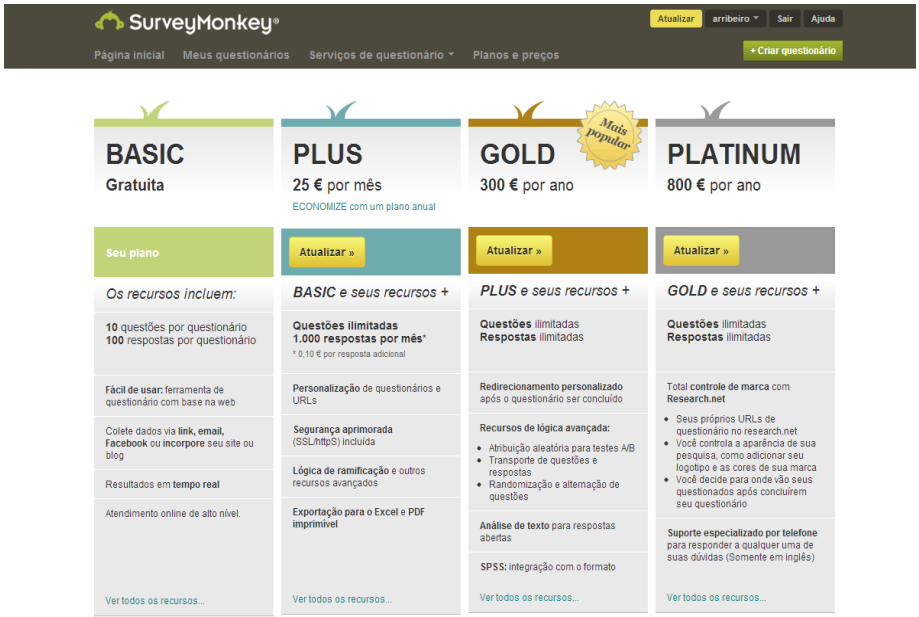


Análise dos resultados

- Exibir resumo
- Procurar respostas
- Filtrar respostas (é possível filtrar respostas por qualquer questão, mesmo as respostas abertas)

- Respostas de referência cruzada (tabulação cruzada das respostas com base em qualquer questão fechada)

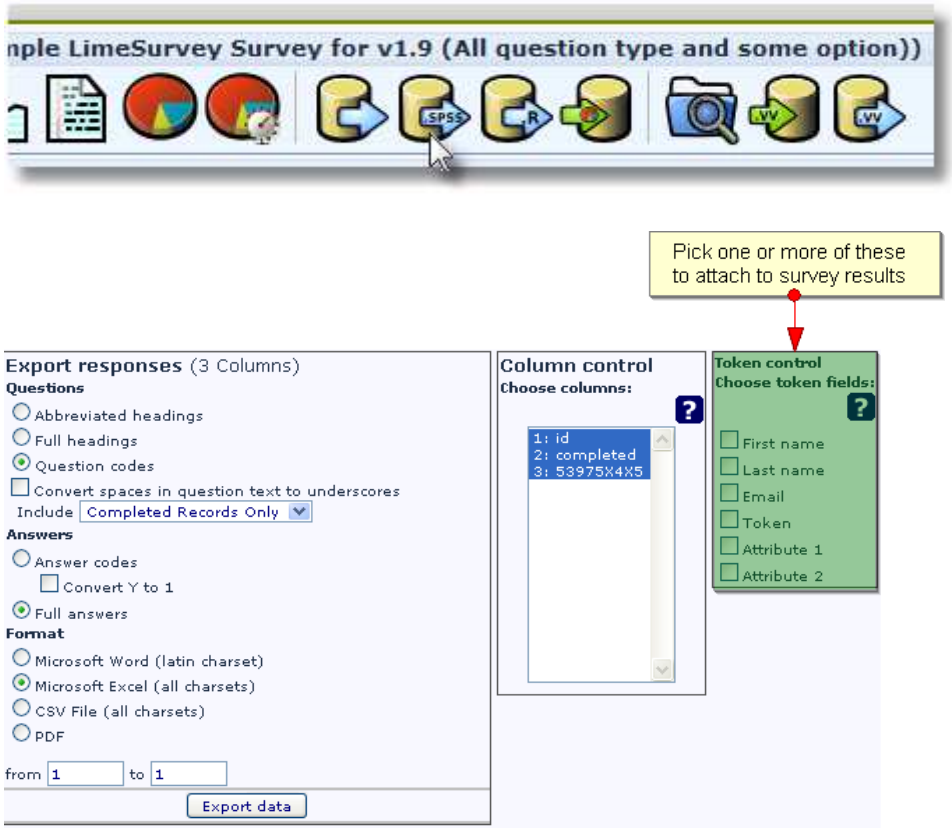
Plano de preços



LimeSurvey

Características

- Criação de questionários
  - 20 Tipos de questões
- Personalização dos questionários
  - Nome, cores, temas
- Gestão de repostas
  - Encerramento do questionário logo que alcançada a data-limite de resposta.
  - Possibilidade de desativar o questionário antecipadamente
  - Possibilidades de os participantes guardarem o questionário e continuarem mais tarde.
- Análise de resultados
  - Análise gráfica e estatísticas básicas
  - Exportação de dados para ficheiros CVS, PDF, SPSS, R, QueXML e MS EXCEL



Construção de um questionário

- Título
- Descrição do inquérito
- Apresentação do questionário por páginas
    - Cada página pode conter um grupo de questões ou a totalidade das mesmas
    - Randomização de página e questão
- Vários templates
- 20 Tipos de questões
- Adicionar questão
    - Tipo
    - Texto
- Lógica de questões
- Opções de design do questionário
    - Numeração de página e questão
    - Barra de progresso
    - Títulos de questionário/ página
    - Botões de navegação
    - Realce de questão obrigatória

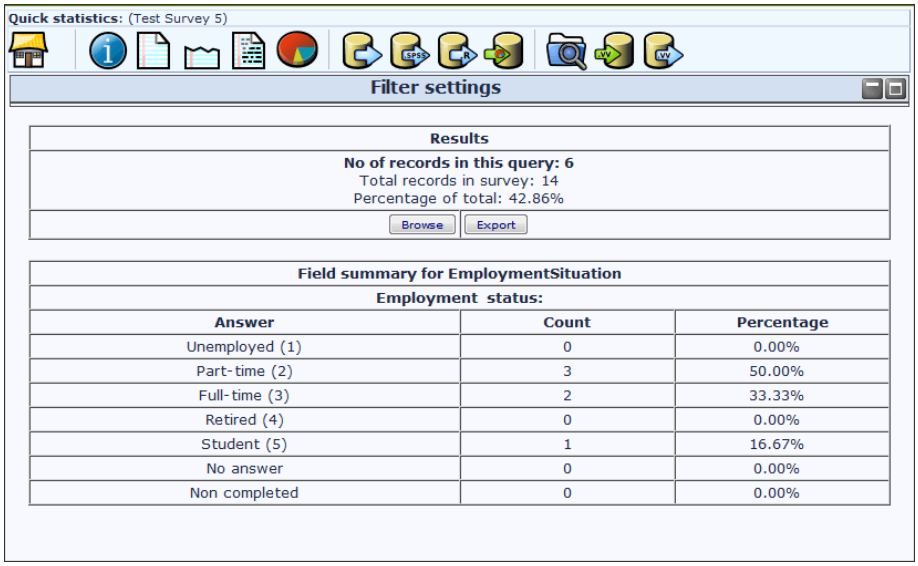
Divulgação do questionário

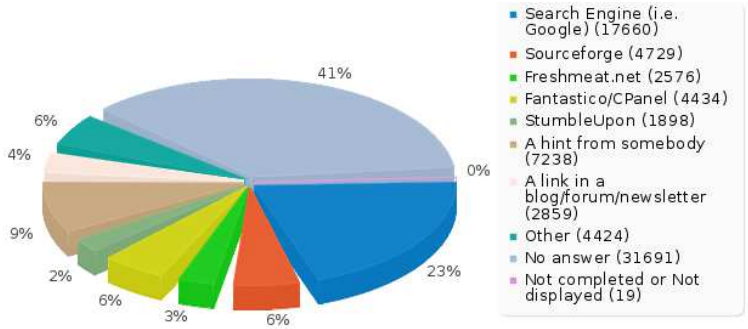
Divulgação por email – envio de convite para participar no questionário.

Envio de um lembrete aos participantes que não acederam ou não completaram o estudo.

Análise dos resultados

- Exibir resumo
- Procurar respostas
- Obter estatísticas a partir das respostas
- Importar/ exportar ficheiros
- Filtrar respostas





Plano de preços

O LimeSurvey possibilita o envio gratuito de 25 questionários por mês, com um número ilimitado de perguntas.

Comparação do SurveyMonkey e do LimeSurvey

Plano básico Funcionalidades/ Programa	**Monkey Survey**	**Lime Survey**
Nº questões por questionário	10	Ilimitado
Nº de questionários	100[1] **Outros planos:** - 25€/mês - 300€/ano - 800€/ano	25 (mês) **Possibilidade de comprar mais respostas:** - 100 respostas/10€ - 250 respostas/35€ - 1000 respostas/60€ - 2500 respostas/125€ - 5000 respostas/200€
Possibilidade de exportação de dados (excel, pdf, HTML)	Não	Sim
Versão para impressão	Não	Sim
Definição de data de encerramento do questionário	Sim	Sim
Possibilidade de agrupar questionários personalizados	Sim	Sim
No mesmo grupo, envio de questionários diferentes para o mesmo destinatário	Sim	Não
Discriminação de respostas	Sim	Sim
Personalização do email de convite	Sim	Sim
Lógica de questão	Não	Sim
Resposta única ao questionário	Sim	Sim
Resumo de resultados	Sim	Sim

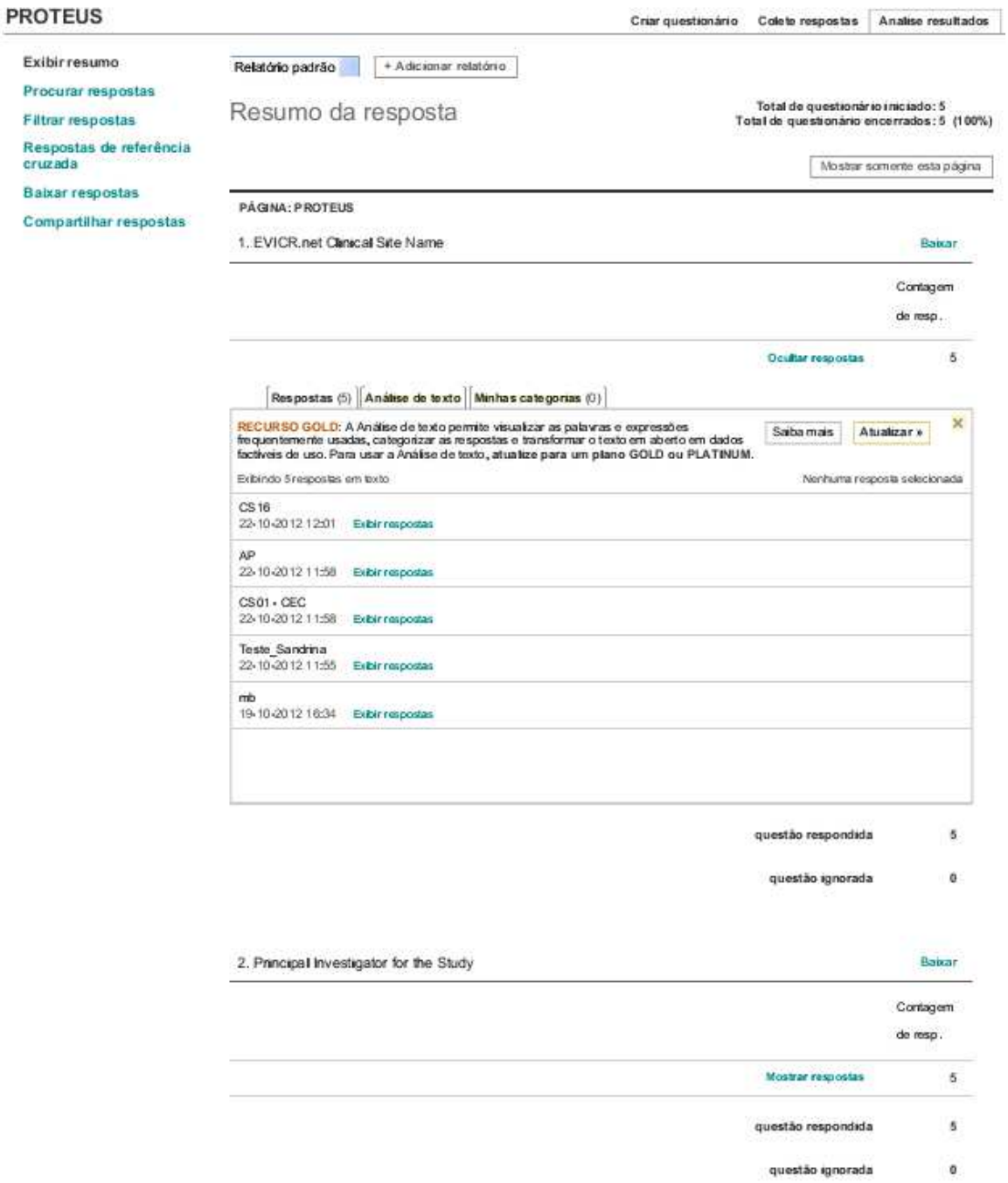
NA – Não Aplicável

[1] Com uma conta básica, só serão exibidas as primeiras 100 respostas de cada questionário.

Anexos

SurveyMonkey

Resumo das respostas



3. Contacts Baixar

		Contagem de resp.
	Mostrar respostas	5
	questão respondida	5
	questão ignorada	0

Mostrar somente esta página

PÁGINA: RECRUITMENT

4. Does your Centre have the capability to recruit at least 8 patients with high risk proliferative diabetic retinopathy according to the inclusion criteria of the Synopsis during a period of 6 months? Criar gráfico Baixar

	% de respostas	Contagem de resp.
Yes	80,0%	4
No	20,0%	1
	questão respondida	5
	questão ignorada	0

Mostrar somente esta página

PÁGINA: EQUIPMENT

5. Is ETDRS visual acuity charts (retroilluminated box) available in your Centre? Criar gráfico Baixar

	% de respostas	Contagem de resp.
Yes	60,0%	3
No	40,0%	2
	questão respondida	5
	questão ignorada	0

6. If you answer yes, select the trademark(s) available in your Centre Criar gráfico Baixar

	% de respostas	Contagem de resp.
Optelec featuring Lighthouse Products	50,0%	2
Precision Vision	50,0%	2
	Other (please specify) Mostrar respostas	2
	questão respondida	4
	questão ignorada	1

Descrição das respostas de um participante

Exibir resumo

Procurar respostas

Filtrar respostas

Respostas de referência cruzada

Baixar respostas

Compartilhar respostas

Relatório padrão

Exibindo 5 de 5 questionados

Tipo de resposta:
Resposta normal

Coletor:
Pre-Feasibility Questionnaire Invitation (convite por email)

Email:
mcosta@aibili.pt

Nome:
Miguel Costa

Valor personalizado:
vazio

Endereço IP:
212.55.146.122

Resposta iniciada:
22 de Outubro de 2012 12:00:41

Resposta modificada:
22 de Outubro de 2012 12:01:26

1. EVICR.net Clinical Site Name

CS16

2. Principal Investigator for the Study

LR

3. Contacts

239480120

4. Does your Centre have the capability to recruit at least 8 patients with high risk proliferative diabetic retinopathy according to the inclusion criteria of the Synopsis during a period of 6 months?

Yes

5. Is ETDRS visual acuity charts (retroilluminated box) available in your Centre?

No

6. If you answer yes, select the trademark(s) available in your Centre

Precision Vision

qwerty

7. Is Frequency-Domain optical coherence tomography available in your Centre?

Yes

8. If you answer yes, select the trademark(s) available in your Centre

Spectralis OCT (Heidelberg)

9. Is Digital Fundus Photography available in your Centre?

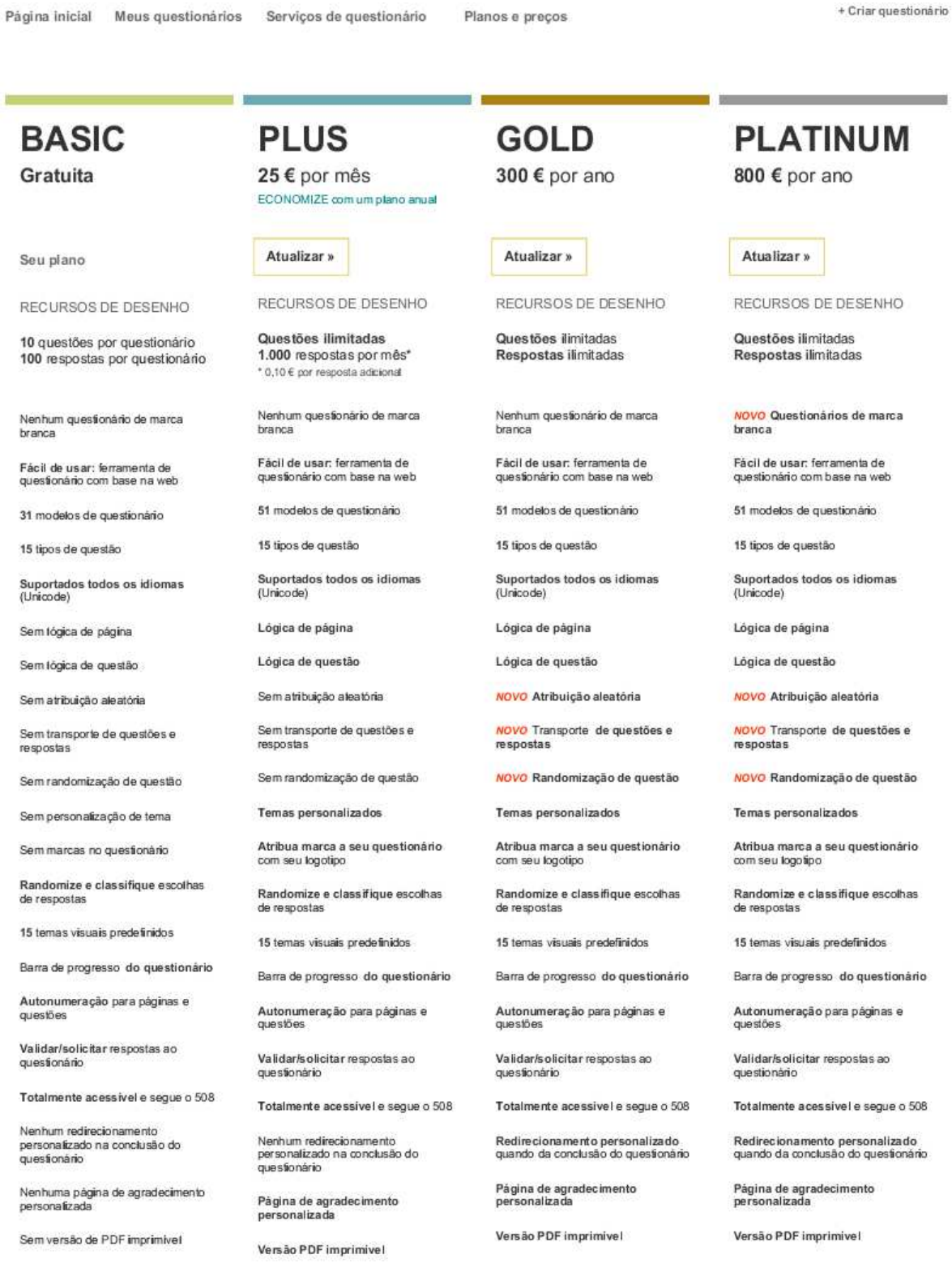
Yes

10. Is Fundus Fluorescein Angiography available in your Centre?

No

qweraweqwr

Descrição dos diferentes planos de preços



BASIC **Gratuita**	PLUS **25 €** por mês ECONOMIZE com um plano anual	GOLD **300 €** por ano	PLATINUM **800 €** por ano
RECURSOS DE COLEÇÃO	RECURSOS DE COLEÇÃO	RECURSOS DE COLEÇÃO	RECURSOS DE COLEÇÃO
Envie seu questionário via link, email ou Twitter	Envie seu questionário via link, email ou Twitter	Envie seu questionário via link, email ou Twitter	Envie seu questionário via link, email ou Twitter
Nenhuma URL personalizada	**URL personalizada**	**URL personalizada**	**URL personalizada**
Compartilhe seu questionário no **Facebook**	Compartilhe seu questionário no **Facebook**	Compartilhe seu questionário no **Facebook**	Compartilhe seu questionário no **Facebook**
Incorpore seu questionário em uma página de seu site	**Incorpore** seu questionário em uma página de seu site	**Incorpore** seu questionário em uma página de seu site	**Incorpore** seu questionário em uma página de seu site
Implemente sua pesquisa por meio de um **pop-up em um site**	Implemente sua pesquisa por meio de um **pop-up em um site**	Implemente sua pesquisa por meio de um **pop-up em um site**	Implemente sua pesquisa por meio de um **pop-up em um site**
Envie sua pesquisa usando nosso **gerenciador de email**	Envie sua pesquisa usando nosso **gerenciador de email**	Envie sua pesquisa usando nosso **gerenciador de email**	Envie sua pesquisa usando nosso **gerenciador de email**
Sem segurança aprimorada (SSL)	**Segurança aprimorada (SSL)**	**Segurança aprimorada (SSL)**	**Segurança aprimorada (SSL)**
RECURSOS DE ANÁLISE	RECURSOS DE ANÁLISE	RECURSOS DE ANÁLISE	RECURSOS DE ANÁLISE
Resultados em **tempo real**	Resultados em **tempo real**	Resultados em **tempo real**	Resultados em **tempo real**
Sem análise de texto	Sem análise de texto	***NOVO*** **Análise de texto**	***NOVO*** **Análise de texto**
Sem integração com SPSS	Sem integração com SPSS	***NOVO*** **Integração com SPSS**	***NOVO*** **Integração com SPSS**
Sem vários relatórios personalizados	**Diversos relatórios personalizados**	**Diversos relatórios personalizados**	**Diversos relatórios personalizados**
Sem filtragem e tabulação cruzada de respostas por critério personalizado	Respostas de **filtro e tabulação cruzada** por critério personalizado	Respostas de **filtro e tabulação cruzada** por critério personalizado	Respostas de **filtro e tabulação cruzada** por critério personalizado
Sem download de respostas	**Efetue o download de respostas**	**Efetue o download de respostas**	**Efetue o download de respostas**
Sem criação e download de tabelas personalizadas	**Crie e efetue o download de tabelas personalizadas**	**Crie e efetue o download de tabelas personalizadas**	**Crie e efetue o download de tabelas personalizadas**
Sem compartilhamento de respostas	**Compartilhe respostas**	**Compartilhe respostas**	**Compartilhe respostas**
RECURSOS DE SUPORTE	RECURSOS DE SUPORTE	RECURSOS DE SUPORTE	RECURSOS DE SUPORTE
Atendimento online de alto nível.	**Atendimento online de alto nível.**	**Atendimento online de alto nível.**	**Atendimento online de alto nível.**
Tempo de resposta alargado	O tempo médio de resposta é de 2 horas ou menos.	O tempo médio de resposta é de 2 horas ou menos.	O tempo médio de resposta é de 2 horas ou menos.
Sem suporte por telefone	Sem suporte por telefone	Sem suporte por telefone	**Suporte especializado por telefone** para responder a qualquer uma de suas dúvidas (Somente em inglês)

LimeSurvey

Resumo das respostas – exemplo de uma pergunta do questionário

Results

Number of records in this query: 1

Total records in survey: 1

Percentage of total: 100.00%

Browse

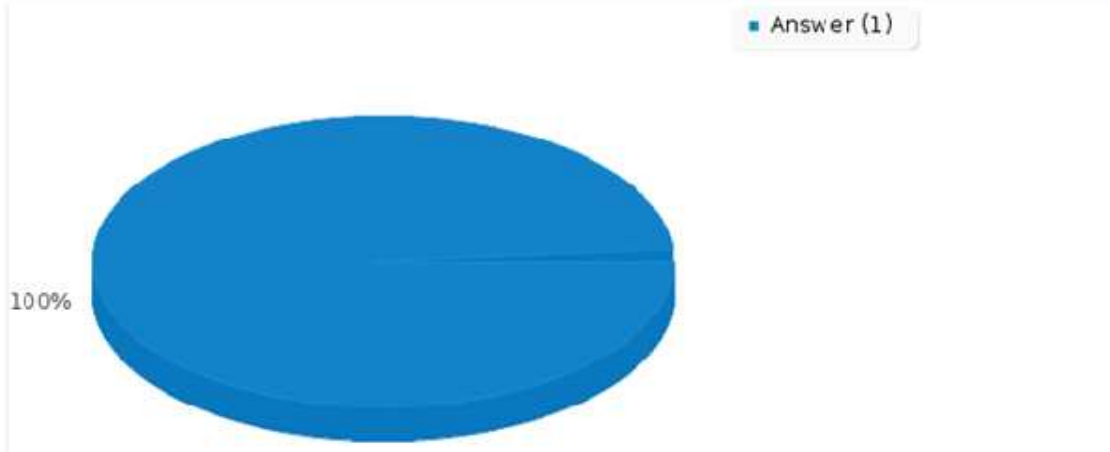
Field summary for G1_Q0001

EVICR.net Clinical Site name

	Count	Percentage
Answer	1	100.00%
No answer	0	0.00%

Respostas

Rita



Descrição das respostas de um participante

NEW RECORD 1

ID:
1
Completed
2012-10-29 10:00:36
Last page seen
3
Language:
en
EVICR.net Clinical Site name
Rita
Principal Investigator for the Study:
ARR
Contacts
arr@aibili.pt
Does your Centre have the capability to recruit at least 8 patients with high risk proliferative diabetic retinopathy according to the inclusion criteria of the Synopsis during a period of 6 months?
Yes
Is ETDRS visual acuity charts (retroilluminated box) available in your Centre?
Yes
If you answer yes, select the trademark(s) available in your Centre.
Precision Vision
[Other] If you answer yes, select the trademark(s) available in your Centre.

Is Frequency-Domain optical coherence tomography available in your Centre?
No
If you answer yes, select the trademark(s) available in your Centre.
[Other] If you answer yes, select the trademark(s) available in your Centre.

Is Digital Fundus Photography available in your Centre?
No
[Comment] Is Digital Fundus Photography available in your Centre?

Is Fundus Fluorescein Angiography available in your Centre?
No
[Comment] Is Fundus Fluorescein Angiography available in your Centre?

First name:
Ana Rita
Last name:
Ribeiro
Email:
arr@aibili.pt
Token:
5usx7tt88ivnb7g

Versão para impressão

Please complete this questionnaire until 30/MAY/2012

Section A: Proteus

Identification

A1. EVICR.net Clinical Site name

A2. Principal Investigator for the Study:

A3. Contacts

Section B: Recruitment

B1. Does your Centre have the capability to recruit at least 8 patients with high risk proliferative diabetic retinopathy according to the inclusion criteria of the Synopsis during a period of 6 months?

Yes ☐

No ☐

Section C: Equipment

C1. Is ETDRS visual acuity charts (retroilluminated box) available in your Centre?

Yes ☐

No ☐

C2. **If you answer yes, select the trademark(s) available in your Centre.**

If you have another model, please specify it

- ☐ Optelec featuring Lighthouse Products
- ☐ Precision Vision
- ☐ Other (please specify)

Other (please specify)

C3. **Is Frequency-Domain optical coherence tomography available in your Centre?**

- ☐ Yes
- ☐ No

C4. **If you answer yes, select the trademark(s) available in your Centre.**

- ☐ Cirrus OCT (Zeiss)
- ☐ Spectralis OCT (Heidelberg)
- ☐ OCT-2000 (Topcon)
- ☐ Other, please specify

Other, please specify

C5. **Is Digital Fundus Photography available in your Centre?**

If yes, please specify the model

- ☐ Yes
- ☐ No

C6. **Is Fundus Fluorescein Angiography available in your Centre?**

If yes, please specify the model

- ☐ Yes
- ☐ No

Thank you for your collaboration!

Appendix II – Lime Survey Manual

VERSION DATE: 2013-05-09

Introduction

LimeSurvey is available at https://www.limeservice.com/en/. You can create an acount by clicking on the “Click here To Sign Up” menu. Next, you must complete the required fields and accept the Terms and Conditions to finish your registration.

After register, you can access your acount by the Login button 

.

Now you can start creating surveys!

A survey has three integral compenents, each of which must exist:

- A survey name;
- Al least one group;
- At least one question.

The survey name provides the unique title to a survey and becomes the handle to access various option settings that applyto the survey as a whole. Settings such as the welcome message on the opening screen, the description of the survey, contact information for the survey administrator and what the format the questions are to be asked.

A survey requires each question to be a member of a group (and only that group). Dependig on the number of questions in the survey, groups can be used to define logical sections, common subject themes or possible pages on the screen. A group can have questions about a similar subject or simply to be setup as a manageable number of questions.

A question group has a title and an optional descrption. You must have at least one group in each survey, even if you do not wish to divide the survey into multiple groups.

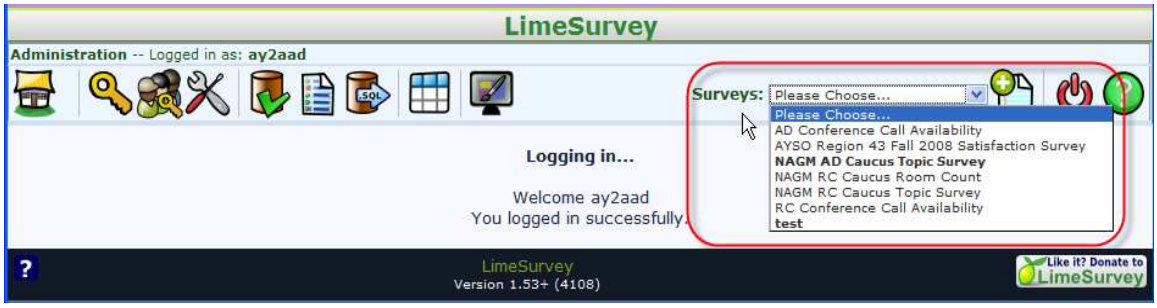
Questions are the core of your survey. There is no real limit to the number of questions you can have in your survey or in a group. Questions include the actual question text as well as settings that determine what form of answer you will accept. You can also specify a short “help” explanation for each questions for each question and determine whether the question is mandatory (that is, must be answered) or optional.

Creating Surveys

The limesurvey tool presents horizontal tool bars to the survey creator in their web browser. These toolbars are the header of a window allowing interaction.

Administrative Tool Bar

The top toolbar is usually the administrative tool bar providing top level, global actions. one of the key items is the drop down list of surveys along with a Create New (survey) button  . Both are on the top right side of the toolbar.



The button provides you an online guide for Limesurvey.

If the Administrative Tool Bar does not appear to be on top, click the home button to get it back. The labelset and Template editors, available in this toolbar, are the only ones that can replace the Administrative Tool Bar.

Survey Tool Bar

Similar to before, one can click on the drop down list of question Groups or on the Create New (Group) button toolbar. Either selection will bring up the question Group toolbar below the survey toolbar.

In this menu you can also test a survey at any point while you are creating it, by choosing the Test Survey button . This allows you to check how the survey looks and feels before you actually initialize it. When testing a survey your responses will not be saved.

- **Survey settings**

There are several settings in Limesurvey that are edited by clicking the "Edit Survey Settings" icon in the "Survey Properties" dropdown menu of the survey toolbar. All survey settings and functions are organized in tabs. It will be mentioned the most important features.

- General
  - Base language- this sets the base language for the survey, once saved, it can not be change later;
  - Title – this is a brief descriptive name of the survey. By default, description is used in the invitation name;

- Welcome message – this allows you to enter a message that will display when a participant first logs into your survey;
- End message – this allows you to enter a message that will display when a participant completes a survey;
- Administrator – this is the name of the contact person who administers the survey; it will be included in emails sent out inviting participants to respond;
- Admin email – this is the email address of the administrator and is used as the "reply to:" address on any emails sent;
- Bounce email – this is the email address where a delivery error notification email should be sent. By default, this is the same as the administrator's email address.

- Presentation and navigation
  - Format
    - Question by question – the survey will display one question per page;
    - Group by group – the survey will display all questions in a group per page;
    - All in one – the survey will display all questions in one single page;
  - Templates
  - Show welcome screen – Yes/No. If yes, then the welcome message defined in Text Elements section will be displayed;
  - Show progress bar: Yes/No. allow the administrator to turn off the progress bar;
  - Show group name and/or group description
    - Show both (default);
    - Show group names only
    - Show group description only
    - Hide both
  - Show "No Answer": Yes/No". When Yes, the No Answer will be displayed as the default option for non-mandatory single-select questions. Be aware that if you switch this off, the participant won't be able to unselect a chosen option in a non-mandatory question;
- Publication and access control
  - Start date/time – set this to some date if you want your survey to start on a special date. The survey will start on midnight of that day and only then will people be able to answer to it.
  - Expiry date/time – set this to some data if you want your survey to expire on a special date. This is the last date on which the public survey will let people participate;
- Notification and data management

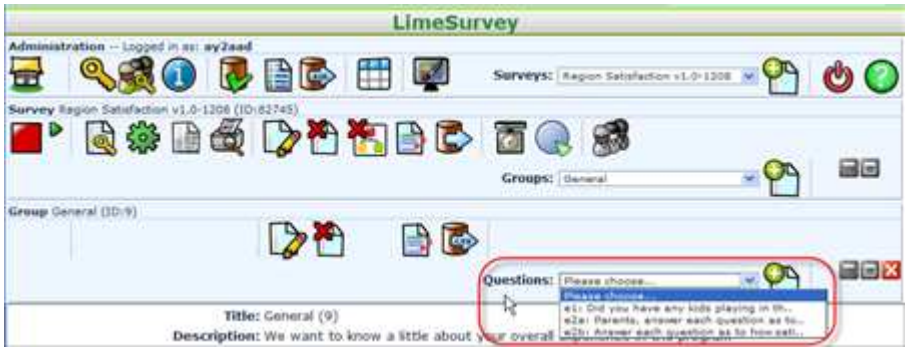
- Send a basic admin notification email to: and Send detailed admin notification email to: these fields will allow you to send notifications or surveys responses to additional email addresses once the survey is submitted
- Date stamp? – This field allows you to determine whether the survey will datestamp all responses. If you choose Yes, then when a response is submitted, a field will be included in that response indicating the time and date that the response was made.
- Save timings – if activate then on survey activation a separate table will be created where the timings for your questions will be saved, e.g. how long a user stays on on page during taking the survey.
- Participant may save and resume later? – this setting allows a participant to save his response and resume to answer the survey at a later time

- Tokens
  - Anonymized responses – this allows you to determine whether responses to your survey are matched up with information from your surveys tokens table, or kept "anonymous". The default is "No". if you choose "Yes" then your survey is set radically anonymize responses – there is really no way to connect answers and participants.
  - Allow editing of answers after completion? – Default: "No". if you activate this setting the participants may return to his survey by clicking the invitation link even if he already submitted the survey. This only works for non-anonimyzed surveys

Group Tool Bar

Groups can be used to group questions in a survey. If you are going to have multiple groups, you should note that by default the survey questions will be displayed group by group.

Groups can also include a "description". This filed allows you to publish an explanatory note for any set of questions. If you add a description, it will be presented at the survey before commencing any of the questions of that group. If you do not include any text here, the public participants will simply move on to the first question in the group with no stop.



- **Adding Questions**

Once you have created your groups, you can start adding questions within each group. Create a new question by clicking on the add icon  to add a fourth toolbar to now edit a Question. When adding a question, the options available are:

- Question code – this code is only for quick identification for a question in export or for evaluation. Try to be consistent with your coding in this field. This field is normally not displayed to people taking the survey.
- Question – this is the actual question being asked. There is no real limit lengh of the question here, however if you want to explain the question, leave that for the "Help" field.
- Help – this is an optional field. It is useful if a question needs some explanation, or you want to explain how it should be answered.. when you put text in this field, a "Question Mark" icon appears on the survey entry screen with the help text right beside.
- Question type: this determines the type of reposnse the survey allows. View the section "Questions" of this manual.
- Validation – this feature is available on all free text type questions ("Short Free Text", "Long Free Text", "Date" or "Numerical"). You can use standard Regular expressions in this field to validate the responses to the question, and if the responses don't validate against this expression, the user will be prompted to ty again before they can progress.
- Other? – depending upon you chosen "Question type" this option may appear. It allows you to specify that an "other" option be presented in some of th list question types.
- Mandatory? – For all question types, except the text ones, this setting allows you to require users to answer the question, before they can move on the next question.
- Relevance – this is the Boolean equation that specifies the conditions for this question. If it evaluates to true, the question is show; otherwise it is hidden and since it is irrelevant, data for that question is nulled in the database.

You can also reorder questions by clicking on the Change Question Order icon  in the group toolbar. You can change this order by sampling click on the "Up" and "Down" buttons. To preview a question click on the Preview Question icon  on the question bar.

Various question types require you to add a list of answers options and/or subquestions. To add answers to one of these questions types click on the  "Add/Edit Answers for this Question" icon in question button bar. Similarly when adding questions, when adding answers you will be asked for:

- Answer code;
- Text – the answer/sub question that will be displayed;
- Sort order – this determines the sort-order of the answers. You can use the "Up" and "Down" buttons next to each answer to change the position of that answer in the list.

The existing question types are:

- Arrays

An array allows you to create subquestions as your left hand headings along the y-axis of a table, and let participants respond with a series of possible answer options using those subquestions along the y-axis of the table. Examples of uses for this type include multiple point choice scales and questions that require feedback on several aspects of a particular topic. The types of arrays available in Limesurvey are:

  - Array
  - Array (5 point choice)
  - Array (10 point choice)
  - Array (Yes/No/Uncertain)
  - Array (Increase/Same/Decrease)
  - Array by column
  - Array dual scale
  - Array (numbers)
  - Array (text)

- Multiple choice questions

  Sometimes you want the participant to mark more than one option in the same question; this is achiving using checkboxes. The types of multiple choice questions available in Limesurvey are.

  - Multiple Choice;
  - Multiple Choice with comments.

- Single choice questions

Single choice questions are those where the participant can only pick a single predefined answer option. The types of sigle choice questions available are:

  - 5 point choice;
  - List (dropdown);
  - List with comment;
  - List (radio)

- Text questions

Limesurvey provides a number of possible variations of the standard text fields.all of these can be defined further using the “Advanced Question settings” which permit to restrict the number of characters as well as the size of the field. Types of text questions are:

  - Short free text;
  - Long free text;
  - Huge free text;

- Multiple short text.

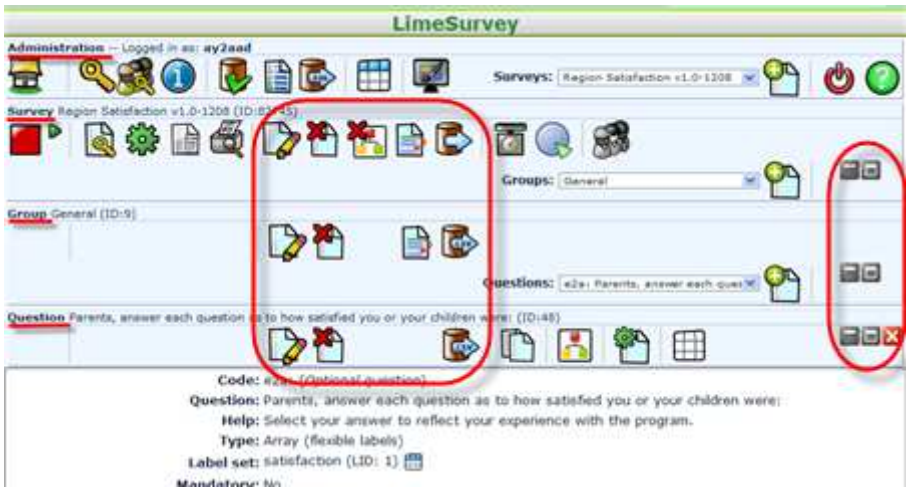
- Mask questions

All questions where the input of answers is predifined are defined as “mask questions”. Examples are:

- Date;
- File upload;
- Gender;
- Language switch,
- Numerical input;
- Multiple numerical input;
- Ranking;
- Text display;
- Yes/No;
- Equation.

Common Buttons

In these nested toolbars are some common navigational buttons. There is an Edit button to edit the object you selected. By default, you will be put in the editor if you create the object. There is a Delete button to delete the object. For Groups and Questions, there is a Reorder button to change the order the object appears in during the survey execution. Finally, there is an Export button to export a survey, question group or question that you can import back into another survey. Note that the Create button also allows you to import a previously exported object.



Finally, there are two to three small buttons to the far right to minimize, maximize and close the window of a toolbar. The maximize button will take you back to the summary window of the currently selected object.

As seems natural, the window of the current toolbar is automatically minimized when you select a lower level object to edit. Only the current toolbar and its window can be closed. You can open a previous toolbar and window by clicking on its maximize button. You can jump around by selecting or creating a new object in another toolbar without having to close the currently open window first.

Sending a Survey

Activating a survey

Once you are happy with the structure of your survey you can activate it by clicking on the "Activate Survey" icon  . Activating a survey does a number of things:

- It creates a separate database table to hold all survey responses, and creates for each possible answer to the survey a filed in the table;
- It allows people to enter data into that table, and gives you access to other features for this survey;
- It gives you access to the "tokens" feature. Once a survey is activated, the tokens button will be available;
- If your survey is set to "not anonymous", a tokens table will be created automatically.

Before you activate a survey you should note that:

- When the survey is initialized you can change the text for questions, answers, the survey, etc. but not the type of question or the type of answer.
- You cannot add new questions or delete questions. Nor can you add answers to any of the array or multiple choice answers – however you can add answers to the basic list type questions.
- If you deactivate (not expire) the survey, it will move the responses to a backup table and lose participation information but you will again be able to add new questions

Once you have activated a survey and are receiving responses it is worthwhile considering the following:

- Export the survey structure  immediately and save the .csv file on a safe place;
- Regularly visit the "browse" screen  and export the received responses and keep c copy of the file.

Participants - Tokens

On many occasions you want to invite a group of people to participate on a survey, keep track of who has completed the survey, and ensure each person can only participate once. The tokens feature allows you to do the following:

- Import a list of names and addresses for participants;
- Generate a unique token number for each participant (invitation code);

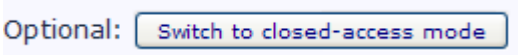
- Send an email invitation to each person in your list who has not yet responded, by group or individually;
- Track who from your list has responded;
- Restrict access against people who have not got a token, and those with a token who have already responded;
- Edit/change any details in your list;
- Create email templates for invitations & reminders.

Once the survey is switched to closed-access mode (you have enabled tokens for this survey), then only the people with a valid token code (not already used) can access the survey.

Activate Tokens

There are two ways to activate tokens:

- After survey activation will be asked if you want to activate tokens



- OR you can click on the tokens symbol  - even before the survey is activated.

The token management tools

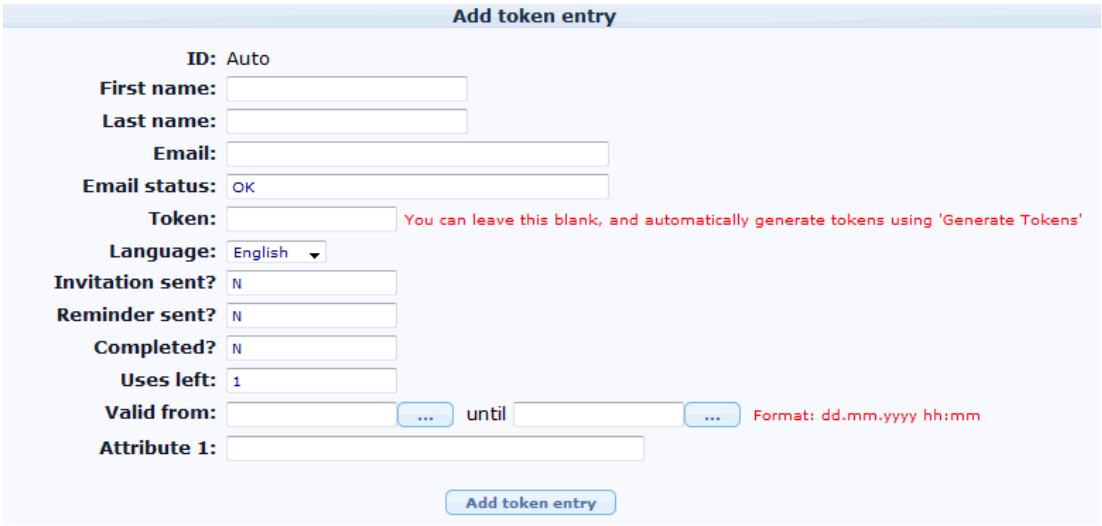
After creating the tokens table you can click on the tokens icon to the token administration. The following section is a brief rundown of the menu options in the tokens screen:

- Admin: returns to the main survey admin screen;
- Summary: displays the complete list of participants in the tokens table (number of tokens, how many have been sent an invitation and how have responded).
- Browse: displays the complete list of participants in the tokens table. From the browse screen you can edit or delete individual entries in the token table as well as perform a number of other useful functions;
- Add new token entry: allows you to add an entry to the tokens table;
- Add dummy token: allows you to add an entry to the tokens table;
- Manage additional field attributes: allows you to add additional fields to the tokens table to store custom participant data;
- Import from CSV: allows you to import information from a CSV file,
- Import from LDAP: allows you to import information from an LDAP query;

- Export tokens to a CSV file: creates a standard CSV (comma delimited) file with a complete list of participants of your current tokens table;
- Edit email templates: used to customize the templates used for the invitations, reminders, confirmations and registrations emails;
- Send email invitation: sends bulk email invitations to all participants in the tokens table who have not already been sent an invitation;
- Send reminder email: sends bulk email reminders to all participants in the tokens table who have not yet responded, but have been sent their first invitation,
- **Generate tokens:** creates unique tokens for all individual entries in the tokens table that do not yet have one;
- Drop token table: delete the token table and set the survey to open-access mode;

Adding a Token

A typical entry contains the following fields:



- First and last name: … of the participant;
- Email: the participant's email address;
- Email status: a field to keep track of bad emails. Marking this token with an email status other than "OK" will help skip this entry when sending invitation or reminder emails;
- **Token:** this is the invitation code. It is usually generated by the "Generate tokens" button;
- Language: if you to set the default language for this participant;
- Invite sent: defaults to "N", otherwise would contain the date when the invitation email was sent;
- Reminder sent: defaults to "N", otherwise would contain the date when the reminder was sent;

- Uses left: a counter of number of times the token can be used;
- Valid from & valid until: you can sent a date/time range where this token would be allowed to use. You can leave this empty if you don't want to limit participation time frame for certain uses. Note: if the user is answering the survey and the participation time ends then the user is locked out immediately and won't be able to finish the survey.

Create Dummy Tokens

- Number of tokens: number of tokens to be added. Default is 100;
- Token length: number of characters or length of token. Default is 15;
- First and last name: … of participant;
- Email: the participant's email address;
- Language: if you want to set the default language for this participant;
- Uses left: a counter of number of times the token can be used;
- Valid from & valid until: you can sent a date/time range where this token would be allowed to use. You can leave this empty if you don't want to limit participation time frame for certain uses. Note: if the user is answering the survey and the participation time ends then the user is locked out immediately and won't be able to finish the survey.

Note that Name, email, language will be set to the same value for all dummy Tokens.

Using the browser screen and editing tokens

The browse screen will show you a list of all entries in the tokens table, as well as giving you some "action" buttons that can perform specific tasks for that individual entry. The top row of the table has three columns: the dialogue on the right gives options for displaying a number of records, and a starting point. In the middle is a search bar and the symbols on the left let you move backwards or forwards through your list.

The second row of the table (see image below) includes various criteria to sort the entries and for each a green arrow that – if clicked – will refresh the screen showing the tokens ordered by that

criterion. The “Actions” column gives a list of specific tasks that can be performed on that individual entry:

- Do the survey using the unique token of this entry;
- Edit this entry;
- Delete this entry;
- Send an invitation/reminder to this survey entry;
- If the survey is not anonymous, another button will appear, allowing you to view the response from this individual entry.

Emailing

- **Field Names**

The following field names are allowed in invitation/reminder email templates and must be entered in the survey properties. When sending out the emails these field names will be already replaced in the preview of your invitation/reminder email.

Field Name	Description
ADMINEMAIL	Email of the Survey admin
ADMINNAME	Name of Survey Admin
SURVEYNAME	Title of your survey
SURVEYDESCRIPTION	Description of your survey

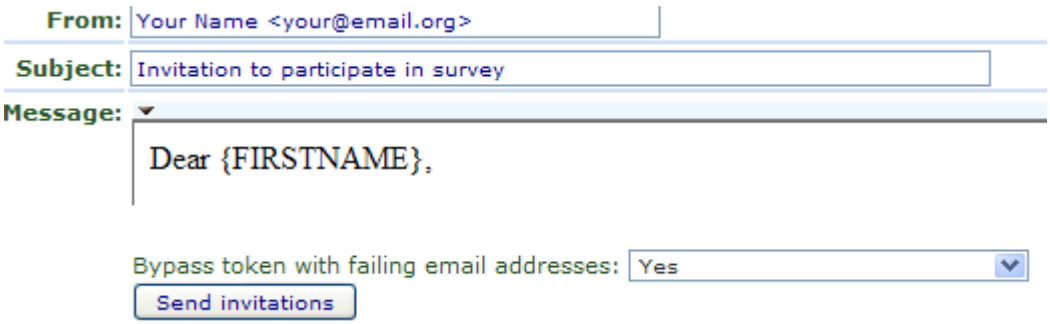
The following field names are allowed in invitation/reminder emails (subject and/or body) and will be replaced while sending out the emails:

Field Name	Description
EMAIL	Email of the recipiente
FIRSTNAME	First Name
LASTNAME	Last Name
SURVEYURL	The URL pointing to the survey start - if you are sending HTML emails this will be a fully linked HTML version
OPTOUTURL	The URL to deactivate sending of mail for this survey - this will be a fully linked HTML version
TOKEN	Token to access the survey

If your survey is NOT anonymous, the following field names are available to insert token data in survey text and javascript:

Field Name	Description
TOKEN:EMAIL	Email of the recipient
TOKEN:FIRSTNAME	First Name
TOKEN:LASTNAME	Last Name
TOKEN	Token to access the survey

- **Send invitations**



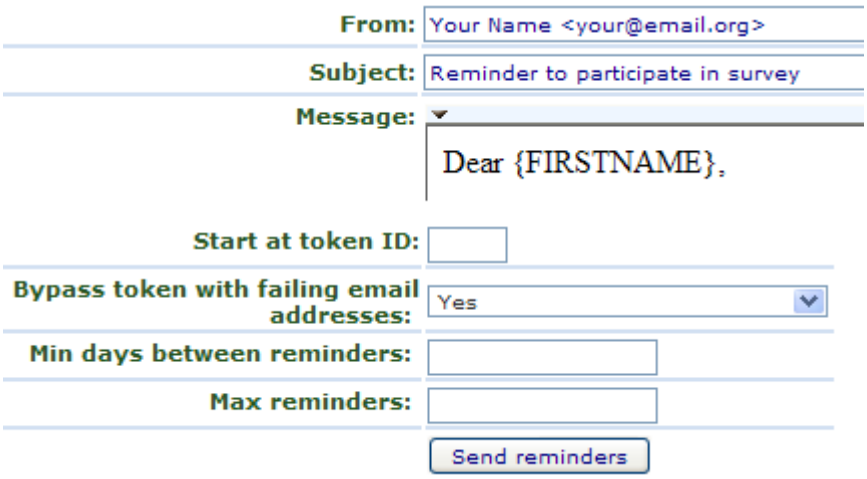
You can skip tokens for which the email status is different from “OK”, by choosing the “bypass token with failing email addresses” option.

- **Participant opt-out**

When you use the OPTOUTURL tag in your invitation/reminder enail, your participants have the possibility to opt out of this particular survey by just clicking on the related URL in the email – so

you do not harass them with reminder emails. A participant that opted out of your survey will have the email status “OptOut” set in the token.

- **Send reminders**



When sending reminders you can:

- Bypass tokens with failing addresses;
- Skip tokens for which an email has been recently sent;
- Skip tokens for which a given number of emails have already been sent.

Note: a reminder will only be send to tokens where the “completed” field is not “N” (this means the respondent has either not taken or has not completed the survey).

- **Confirmation email**

If you are using tokens and a participant fills out the survey, a confirmation email is sent to his/her email address. If you do not want this message to be sent, remove all content from the “Confirmation Email Subject” and “Confirmation Email” fields.

Survey Results

Closing a survey

There are two ways for closing a survey: Expiry or deactivation.

Expiry (edit the survey details and set an “Expiry Date”):

- No results lost;
- No respondent information lost;
- Change of questions, groups and parameters is limited;
- An expired survey is not accessible to participant (they only see a message that the survey has expired);
- It is possible to perform statistics on responses inside limesurvey.

Deactivation (click on “deactivate this survey” in the administration panel)

- All results lost;
- All respondent information lost;
- An expired survey is not accessible to a respondent (only a message appears that you are not permitted to see this survey);
- All questions, groups and parameters are editable again.

In case you accidentally deactivated you survey, it is important you do not change anything in the survey. Then you can activate your survey again. You go to the “Browse responses for this survey” menu. Click the “Important answers from a deactivated survey table” button. Next you can choose your survey table and click on the “import responses” button.

Browse results

When survey responses have been submitted, you will want to be able to view those responses, maybe edit some of them (or possibly delete some), export them, and get some information about the responses received so far, and so on. All of this is done through the browse function.

When a survey is active, a browse function will appear in the Survey information portion of the main admin screen.

The main screen (Survey Summary) gives you the total number of responses recorded (full response and incomplete responses). Other options available in this screen are:

- Admin: Return to the admin screen for surveys;
- Survey summary: just show the total responses so far (initial screen);
- Browse all: Display all the results to the survey (mote: the browse shows full descriptive question names, but only abbreviated answers);
- Browse last 50: Display the last 50 responses to the survey, ordered from most recent to least recent;
- Data entry: go to the data entry screen to add a new survey;
- Printable version: printable version of the survey to be filled by hand;
- Statistics: a simply method for filtering and getting summaries of responses;

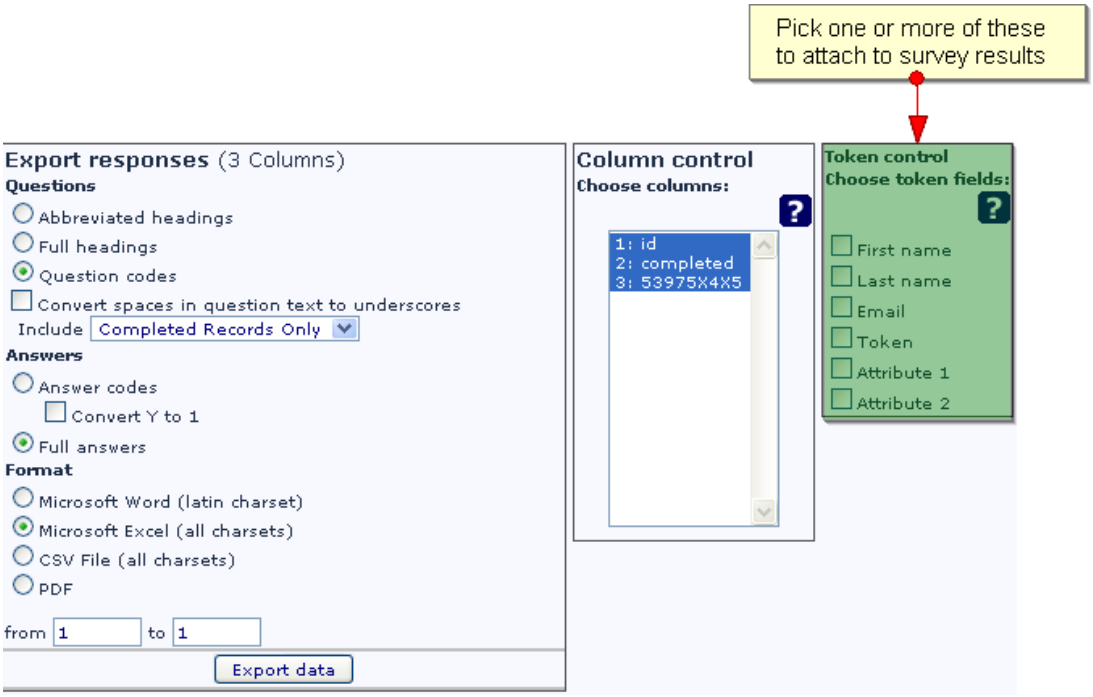
- Export data: export all the responses to this survey to a Word, Excel or CSV file;
- Backup survey X results: dump the table structure and contents to a standard CSV file.

- **Export data to application (Excel/.csv)**

On top of the browse responses page several export options are listed, beginning with “export to CSV/application”.

When exporting results to an application there are several filter options which are separated into:

- General
  - Set a range like export records X to Y;
  - Set to export all records, incomplete records only or incomplete records only;
- Questions
  - Set how the heading should look like: Abbreviated heading, full headings or question codes;
  - Convert spaces in question text to underscores;
- Answers
  - You can either export full answers or convert answers codes Y and N to a defined variable;
- Format
  - Microsoft word;
  - Microsoft excel;
  - CSV file;
  - PDF;
- Column Control
  - Set which answers should be exported;
  - Set which token data should be exported. This option is only available if your survey is not anonymous.



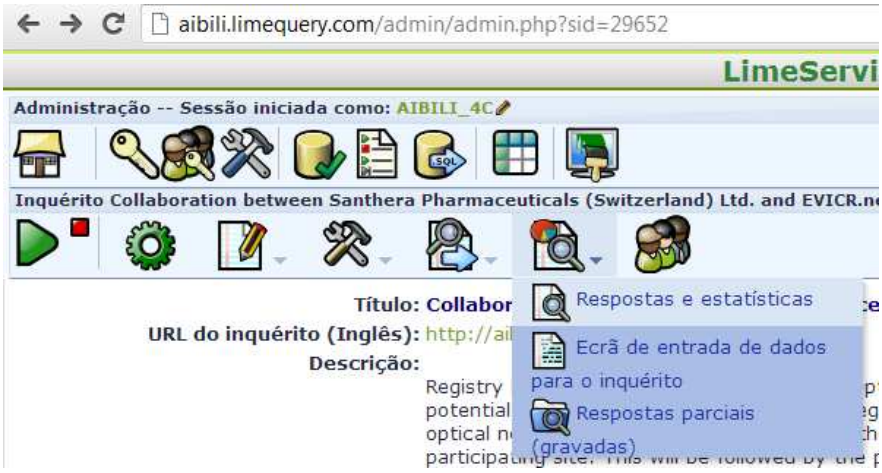
- **View survey results by participant**

In order to view individual participant choices (and not the report regarding the whole survey), browse to: browse responses – display responses – click on one IDs in the left column. Participants can be identified either by token, name or IP address.

- **Editing and deleting responses**

When viewing your responses, you will be able to view a specific response by clicking on the ID number. From this point you can choose to Edit or Delete this response.

Statistics



The statistics feature allows you to filter your data and retrieve numbers and summaries of different fields from it.

When you click the “Get statistics” button you will be presented with a list of all available questions. For each question there is a checkbox that can be selected in order to show a summary table. To view the results for a question or questions, select the checkbox(es) at the top of the question(s) and then click “View stats”. Alternatively, to view the results for all available questions, check the “View summary of all available fields” box at the very top and then click “View stats”.

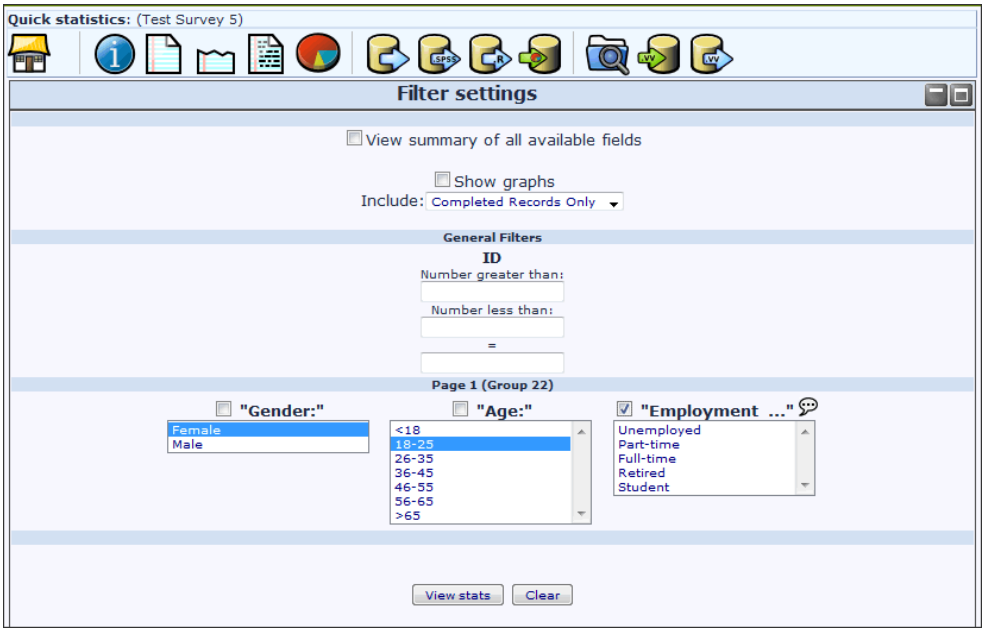
You will then be given a “Results” table which will indicate the number of cases and a “Field Summary” table for each question selected which will summarize all possible answer in the question(s), their totals and percentages.

- **Filtering data**

Data can be filtered in several ways:

- By survey completion – use the dropdown at the top to select Completed, Incompleted or All Records;
- By ID – use the inputs to filter by ID number;
- By text – you can search the responses to a free text question type (and similar types) by entering a text.

Selecting “View stats” will then give you the Results table, indicating the number of responses matching your criteria, and a Field Summary table for each question selected which will summarize all possible answers in the question(s), their totals and their percentage.



- **Browsing/ exporting filtered results**

If you want to export the responses that match your criteria, click on the “export” button of the “Results” table. This will bring up the usual export screen, however when you export the results

you only receive the responses that match your criteria. Similarly, click on the browse to view the matching responses in the browse screen.

Data entry

Open the Data Entry Screen by clicking on the  Data Entry Screen. This function is intended as a data entry system for paper based surveys. The Data Entry Screen is intended to be used when entering returned surveys on a mass basis and subsequently is designed to allow for keyboard based entry.